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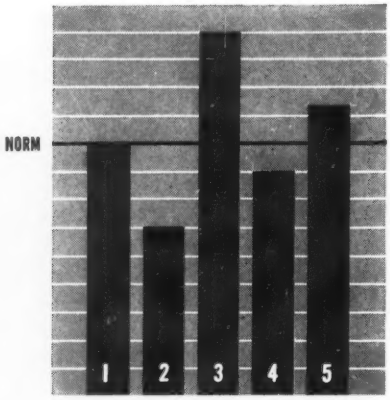

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THE USE OF RADIOIODINE IN THE TREATMENT OF EXOPHTHALMIC GOITER*

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IN 1942 Hamilton and Lawrence (1) and Hertz and Roberts (2) reported on the treatment of hyperthyroidism with radioiodine. The restricted availability of radioiodine and dislocations produced by the war prevented widespread extension of its use, either as a tool for the study of thyroid physiology or as a diagnostic or therapeutic agent. However, in 1946 Hertz and Roberts (3) reported their experiences in the treatment of 29 cases of hyperthyroidism and Chapman and Evans (4) reported their experiences in the treatment of 22 cases of hyperthyroidism. Both groups used, in treatment, a mixture of about 90 per cent I^{130} (half-life, 12.6 hours) and about 10 per cent I^{131} (half-life, eight days). Both groups reported that radioiodine was effective in the control of hyperthyroidism.

In 1946 the Clinton Laboratories of the Manhattan District, U. S. Engineers, made available for clinical and laboratory use I^{131} (half-life, eight days) produced in quantity in the uranium chain reacting pile. Many

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This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1949. All articles in the September issue of the *Journal of Clinical Endocrinology* will also be included.

groups to whom radioiodine had not been available formerly began studies of its use as a diagnostic and therapeutic agent, as well as a tool for studying the function of the thyroid. Rawson and McArthur (5) have published an extensive review of the work done with it through 1946.

ESTIMATION OF DOSAGE

The estimation of the dose of radioiodine required to produce a therapeutic effect is made complex by a number of physical and biologic factors. The technical aspects of this problem have been discussed elsewhere by Chapman and Evans (4), by Marinelli (6) and by Marinelli, Quimby and Hine (7). The purely physical factors which must be taken into account in estimating dose include the nature and energies of the radiations produced by a given isotope and its rate of decay or half-life. Biologic factors include the concentration of the isotope within the tissue to be irradiated and the rate with which the isotope is lost or secreted from that tissue. In the case of the thyroid an approximation of the dosage of radiation received from radioiodine can be expressed in roentgen equivalents provided that the weight of the thyroid, the quantity of iodine fixed in the thyroid and the rate at which the iodine disappears from the gland can be determined.

When the first therapeutic applications of I^{131} were made in 1946, the only basis for estimating the quantity to be used was the experience of Hertz and Roberts and of Chapman and Evans with a mixture of I^{130} and I^{131}. The effects of this isotopic mixture had been ascribed by these observers largely, if not entirely, to the I^{130} (half-life, 12.6 hours) which it contained. A dose of this isotope delivers 99 per cent of its radiation within a period of three and a half days, whereas a quantity of I^{131}, which could deliver a similar amount of radiation, would require about fifty-two days to deliver 99 per cent of its radiation. In the space of three and a half days, the quantity of I^{130} likely to be lost or secreted from the gland can be regarded as inconsequential, but the loss of I^{131} from the thyroid in the corresponding period of fifty-two days might result in the secretion of a significant proportion of the dose. Furthermore, although the effect of rate of irradiation on therapeutic effect remains a somewhat controversial question, it appeared reasonable to expect that, owing to its slow rate of delivery, I^{131} would prove less effective, unit for unit, than equivalent amounts of I^{130}. The foregoing considerations led us to expect that larger quantities of I^{131} would be required than would be anticipated from comparison with the physical characteristics of I^{130} alone.

A further obstacle to accurate estimation of dose was the fact that estimates of the weight of the thyroid obtained by palpation of the neck are crude at best and particularly so in patients who have recurrent exophthalmic goiter.

Fortunately it was found that the proportion of a therapeutic dose which would be fixed in the thyroid could be predicted with reasonable accuracy if a tracer dose of 100 microcuries was first given and the urinary excretion of fractional amounts of this dose was determined for seventy-two hours (8). Later observations with *in vivo* measurements of the quantity of radioiodine collected by the thyroid, as well as comparison of the results of tracer doses and therapeutic doses have confirmed the relative accuracy of this method.

The third biologic factor which determines dose, namely, the subsequent rate of secretion of fixed radioiodine from the thyroid, cannot be anticipated with certainty, even by *in vivo* studies of tracer doses, since it appears that one of the early and variable effects of a therapeutic dose is an increase in the rate at which radioiodine leaves the gland.

Initial attempts to estimate dose gave only approximations, and an effort was made to keep the doses low enough so that unnecessarily large quantities of radiation would not be administered. In the first cases, we attempted to select a dose which would allow the thyroid to collect approximately 100 microcuries per estimated gram of tissue. It soon became apparent that larger doses were probably desirable for the type of condition being treated and accordingly the dose selected was soon increased so that the thyroid could collect 200 to 250 microcuries per estimated gram of thyroid tissue. Dosage was calculated by the following formula:

$$\frac{\text{Microcuries desired per gram of tissue} \times \text{Estimated weight of thyroid in grams} \times 100}{\text{Per cent of } I^{131} \text{ tracer collected by thyroid}^1} = \text{Desired total dosage in microcuries.}$$

In nearly all instances, the figure employed for the denominator of the equation, that is, the percentage of the I^{131} tracer collected by the thyroid, was assumed to be the proportion of the dose which was not recovered in the urine. Since a variable quantity (about 10 per cent) of the dose usually cannot be accounted for either in urine or thyroid, the dose actually delivered to the thyroid was presumably smaller by a factor of about 10 to 15 per cent than the formula would indicate. However, since the estimated dose was at best no better than an approximation, this factor was ignored. Measurements following the therapeutic dose showed in nearly every instance that the quantity delivered to the thyroid was reasonably close to that intended.

It would be preferable, if circumstances permitted, to express dosage

[1] In the formula the percentage of the tracer dose of I^{131} collected by the thyroid is written without transposition of the decimal point. For example, if 80 per cent of the tracer dose is collected by the thyroid, the denominator of the formula then is 80.

entirely in terms of irradiation; that is, in roentgen equivalents. A concentration of 1 microcurie of I^{131} per gram of tissue will deliver approximately 12 roentgen equivalents the first day and, provided that it is not lost or secreted and that the iodine is uniformly distributed in the thyroid tissue, a total of approximately 160 roentgen equivalents by the time it is entirely decayed. However, owing to uncertainties of estimating weights of the thyroid, the figures for dosage, no matter how expressed, cannot be more than approximations and unless tedious measurements are undertaken for weeks, the rate of secretion from the gland cannot be determined with accuracy. On this account we have intentionally avoided expressing dosage in terms of roentgen equivalents. The values, given in microcuries per gram, can be translated to their approximate corresponding values in roentgen equivalents, if one cares to assume that an average rate of secretion will give a net dose of approximately 130 roentgen equivalents per microcurie per gram of thyroid tissue. On this basis a dose of 200 microcuries per estimated gram of thyroid might represent a total radiation dose of approximately 26,000 roentgen equivalents, substantially all of which will have been delivered in a period of six weeks.

CHOICE OF PATIENTS FOR TREATMENT WITH RADIOIODINE

At the time we began using radioiodine in the treatment of exophthalmic goiter, concern had been expressed regarding possible late effects on the thyroid gland of large amounts of radiation. Also it was not known whether or not the administration of large amounts of the isotope would have a deleterious effect on other organs, in particular the kidneys and whether the gonads might be subjected to sufficient radiation to cause genetic effects (9). These factors cannot be accurately evaluated even now, nor will the answers to these questions be clearly known for some time. Although the fears were to some degree speculative, we decided to give therapeutic doses of radioiodine only to those persons for whom the risk and the difficulties of other methods of treatment appeared to us to be excessive. We have treated with radioiodine patients who had serious heart disease or other complications which would add considerably to the risk of surgical treatment and patients who had recurrent exophthalmic goiter. It was used for recurrent exophthalmic goiter particularly if multiple resections of the thyroid had been performed previously, if unilateral paralysis of the vocal cords was present or if extremely small amounts of thyroid gland remained. Our series of patients represents, therefore, a group who had a severe condition and in many of whom the disease had proved resistant to usual forms of treatment. It is possible that this fact may be of importance in comparing our dosages and results with those in other series of cases.

At this time we are reporting on 40 patients who were treated with radioiodine for exophthalmic goiter at the Mayo Clinic between September, 1946, and February, 1948. We are not including data on a patient who left our observation six days after receiving a therapeutic dose of radioiodine, another who died at home of cardiac decompensation several days after treatment and who had not returned to the clinic for observation and some who have not yet returned for observation since receiving their therapeutic doses. We are not including any case in which the clinical diagnosis was adenomatous goiter with hyperthyroidism, as these cases constitute a separate group so far as collection of I^{131} and other problems of treatment are concerned. We are including in this report those cases in which a diagnosis of exophthalmic goiter with adenoma was made. Our series of these cases is very small and longer observation is required before conclusions can be drawn from it.

Of the 40 patients, 13 were men and 27 were women. The average age of the men was 45.9 years and of the women, 52.0 years. The ages of the men ranged from 30 to 65 years and of the women from 30 to 73 years. Twenty-eight of the patients had recurrent exophthalmic goiter and from one to four attempts had been made to control the disease by surgical resection (Table 1). In some instances the presence of one paralyzed vocal cord in a patient with a considerable quantity of thyroid tissue on the opposite side was the chief reason for deciding on treatment with I^{131}. In 17 cases serious heart disease was present and in some of these, recurrent exophthalmic goiter was present. In some cases the heart disease was of such severity as to cause the estimate of surgical risk to be excessively high. One patient had an inoperable brain tumor and one had developed exfoliative dermatitis from previous use of iodine.

RESULTS

A result was considered good if the basal metabolic rate was lowered to plus 15 per cent or further and if the clinical evidences indicated that the patient was in a euthyroid state (Fig. 1). Results were classified as fair when the severity of hyperthyroidism was markedly reduced by treatment (Fig. 2).

Good results were obtained by the administration of one therapeutic dose of I^{131} in 27 of the 40 cases. In all these cases the clinical evidences of hyperthyroidism were completely controlled by the treatment. In all but 1 case the size of the thyroid was reduced to, or nearly to, normal. Myxedema developed in 7 patients and in these, treatment with desiccated thyroid was instituted. It is not known at present whether the myxedema is permanent or not. Three patients who had good results initially had subsequent recurrences of exophthalmic goiter (Fig. 3); one of them exhibited an in-

TABLE 1. DATA ON 40 CASES OF EXOPHTHALMIC GOITER

Case	Age (yrs.), and sex	Recurrent exophthalmic goiter	Operations on thyroid	Basal metabolic rate before treatment, %	Estimated weight of thyroid before treatment, Gm.	Dose of I^{131}, microcuries per gram	Approximate time from administration of I^{131} to basal metabolic rate nearest normal (months)	Basal metabolic rate after treatment, %	Estimated thyroid weight, after treatment, Gm.	Second dose of I^{131} microcuries per gram	Approximate time from second dose of I^{131} to basal metabolic rate nearest normal (months)	Basal metabolic rate after second dose of I^{131}, %	Estimated weight of thyroid, after second dose of I^{131}, Gm	Time of follow-up, months after first dose of I^{131}	Comment
1	51 F	+ +	2	+33	20	188	2½	− 1	10					4	Myxedema developed
2	37 M		1	+43	10	206	2	− 1	5					6	Recurrence; treated with Lugol's solution
3	47 F			+50	25	211	3½	−13	NP*					4	Myxedema developed
4	59 M			+27	20	272	1	+ 1	NP					7	Clinically euthyroid
5	55 F	+	3	+22	15	182	3	0	P†					11	Recurrence; treated with I^{131}
6	56 M			+41	25	366	3	−11	NP					9	Lugol's solution given
7	37 M	+	2	+25	30	237	3	+13	NP					3	Myxedema developed
8	43 F			+36	40	200	2½	−14	20					6	Clinically euthyroid
9	53 F	+	3	+47	15	574	12	− 3	NP					12	Recurrence; treated with I^{131}
10	31 M			+19	30	88	½	− 2	P					2	Lugol's solution given
11	33 M	+	1	+30	20	110	½	0	NP					6	Brain tumor; Lugol's solution given
12	33 F	+ +	2	+34	30	158	1½	− 9	5					6	Recurrence, B.M.R. +23 per cent; control with Lugol's solution
13	55 F		2	+18	25	215	2	− 8	P					6	Myxedema developed
14	66 F			+40	20	148	5½	+ 8	P					2	
15	51 F	+ + +	1	+44	20	321	2	− 6	10					5½	Mild myxedema (?)
16	30 F		1	+18	15	229	3½	0	NP					4½	
17	62 M		1	+36	40	522	1	− 6	NP					6	
18	43 F			+41	15	297	3½	− 2	NP					5	Myxedema developed
19	61 F	+ + +	1	+19	15	196	3	−12	10					4	
20	58 F		3	+46	35	171	3	−11	P					6	
21	30 M	+ + +	1	+42	40	108	2	− 1	NP					4	
22	36 F	+ +	2	+37	40	225	2½	+ 6	35					6	Myxedema; radiation sickness (?)
23	34 M	+ + +	1	+36	15	252	3	−23	P					3½	Gland not reduced in size
24	72 F	+ + +	1	+31	10	378	3½	+ 5	5					3	Myxedema
25	55 F	+	1	+24	50	252	3½	0	10					8½	

TABLE 1—(*continued*)

Case	Age (yrs.), and sex	Recurrent exophthalamic goiter	Operations on thyroid	Basal metabolic rate before treatment, %	Estimated weight of thyroid before treatment, Gm.	Dose of I^{131}, microcuries per gram	Approximate time from administration of I^{131} to basal metabolic rate nearest normal (months)	Basal metabolic rate after treatment, %	Estimated thyroid weight, after treatment, Gm.	Second dose of I^{131} microcuries per gram	Approximate time from second dose of I^{131} to basal metabolic rate nearest normal (months)	Basal metabolic rate after second dose of I^{131}, %	Estimated weight of thyroid after second dose of I^{131}, Gm.	Time of follow-up, months after first dose of I^{131}	Comment
26	54 M			+38	20	194	2½	0	NP					2½	
27	44 F	+	4	+37	25	201	2½	+ 2	10					6	Myxedema developed
28	56 M	+	1	+40	45	184	4	+13	10	192	6	− 5	P	10	
29	58 F	+	1	+41	35	180	1½	+31	10	80	2	+ 9	P	10½	Lugol's solution reduced B.M.R. to −17 per cent
30	58 F	+	1	+57	35	309	2½	+18	25	128	3½	+ 5	15	8	
31	63 F	+	1	+15	30	91	2	+15	10	42	¼	0	Less than 10	8¼	
32	65 M			+30	50	494	3	+12	25					3	Fair result
33	42 F	+	1	+19	15	184	2	+15	—					2	Poor result; incomplete‡
34	54 F	+	2	+30	40	65	1½	+35	40	54	1½	+43	30	3	Poor result; incomplete
35	45 M	+	2	+43	40	101	2	+ 3	10	93	3½	+14	P	9	3rd dose of 160 microcuries per Gm. controlled; B.M.R. +8%
36	73 F			+29	20	218	3½	+17	NP					3½	Fair result; clinically euthyroid
37	56 F			+41	50	224	1	+39	50					1	Poor result; severe hypertension; diagnosis (?)
38	47 F	+	1	+51	20	334	2½	+20	NP	270	¾	+20	NP	3½	Fair result§
39	52 F	+	1	+59	40	162	1	+48	30	53	3	+12	35	10	1st dose, poor result; 2nd dose, fair result; clinically hyperthyroid
40	54 F			+29	20	119	2	+27	P					2	Poor result; severe heart disease

* NP means not palpable.
† P means palpable.
‡ Later reported to be well.
§ Later observed to be well; B.M.R. −5 per cent.

crease in the size of the thyroid. In 2 of these patients the administration of Lugol's solution (strong solution of iodine, U.S.P.) was all that was needed to control the recurrence. In the other a second therapeutic dose of I^{131} was given. This was done so recently that the result is not known. It must be kept in mind that what we term a good result indicates a result of very short duration and that no final determination of the effect of any treatment in exophthalmic goiter can be judged until it has been in use for many years. Recurrences have followed surgical treatment, for example, as long as forty years after the operation; this occurred in 1 case in the present series.

Results were fair in 8 cases in this series. In all 8 there was significant improvement after the first dose of I^{131}, and in 4 of these a second therapeutic dose resulted in complete control of hyperthyroidism. In 1 case a third dose controlled the disease; in 1 case the result of the second dose was fair. In the other 2 cases the results of a second dose of I^{131} are not known.

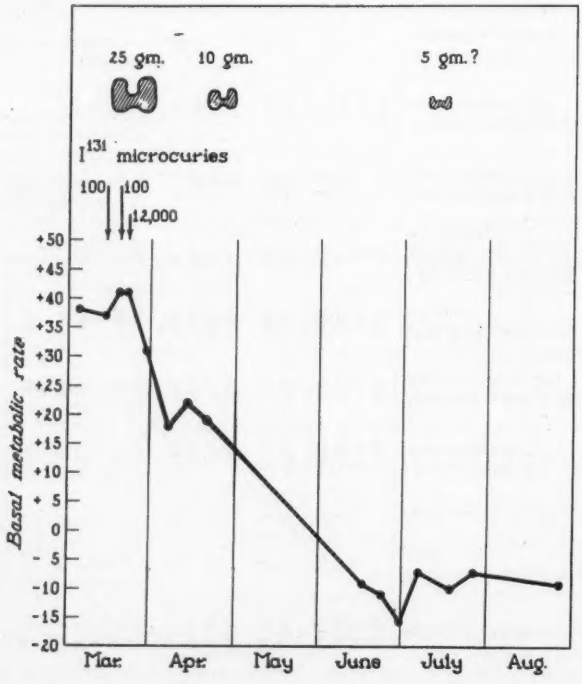

FIG. 1. Example of a good result following treatment with I^{131}. The decrease in the size of the thyroid in four months should be noted. Myxedema developed subsequently.

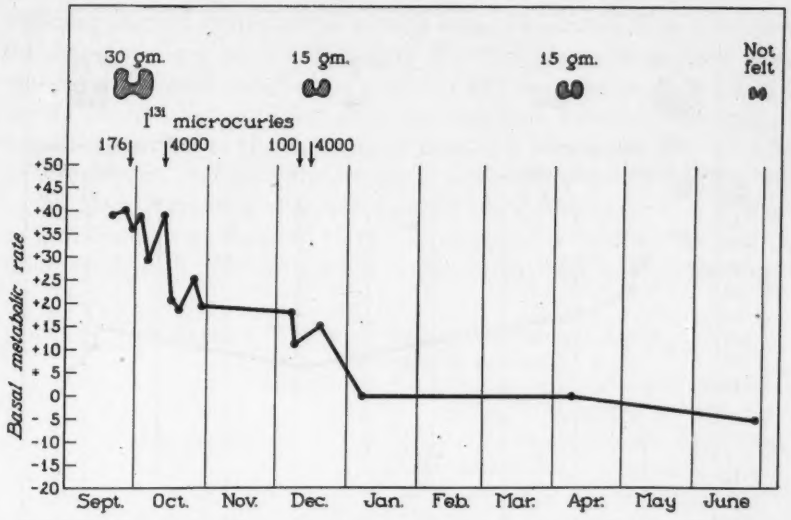

FIG. 2. Example of a fair result following treatment with I^{131}. One therapeutic dose of radioiodine produced improvement but hyperthyroidism was still present two months later. A second dose of I^{131} was given. The decrease in the estimated size of the thyroid should be noted. This patient has remained well for sixteen months.

Poor results were recorded in 5 cases in this series. In 1 case a second dose produced fair results. In another (that of the first patient we treated) two therapeutic doses were given. These we now know were inadequate. The patient refused further treatment. In 2 cases serious heart disease was present and the diagnosis of exophthalmic goiter in each was somewhat doubtful. One patient left our observation immediately after the therapeutic dose was given and reported by mail that she was unimproved and that her basal metabolic rate had not been reduced.[2]

The basal metabolic rates of the various patients before and after treatment are listed in Table 2 and the size of the thyroid glands in Table 3.

The time needed to bring the basal metabolic rate to normal varied greatly. In most cases in which good results were obtained, the basal metabolic rates reached normal levels about six to twelve weeks after treatment was started. In some the basal metabolic rate continued to fall for a longer time.

DOSAGE RECEIVED

As previously stated, in the majority of cases we have tried to administer a dose that would allow the collection by the thyroid of approximately 200 to 250 microcuries for each gram of estimated thyroid weight. The doses

[2] She later reported by mail that she was well.

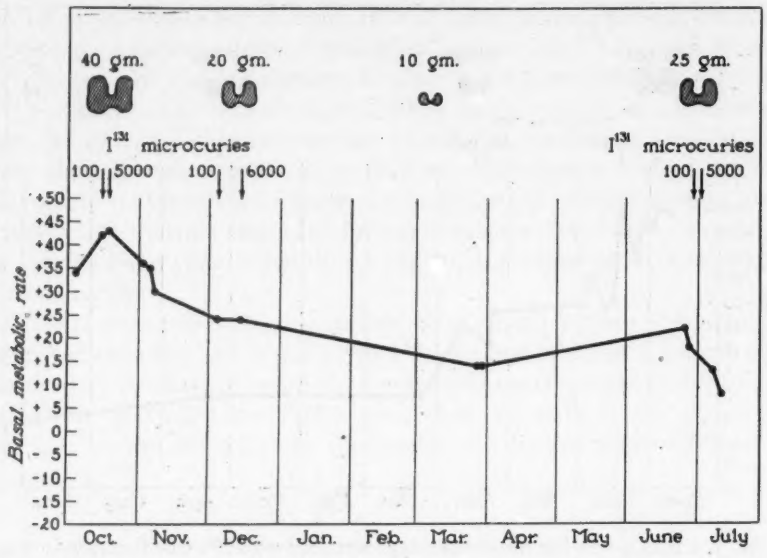

FIG. 3. Example of recurrence following treatment with I^{131}. After one dose the patient became euthyroid and the thyroid shrank to normal proportions. The result was interpreted as good. Subsequently the thyroid again enlarged and hyperthyroidism developed: a second dose of I^{131} was required.

given by mouth to the patients in this series varied from 2,600 to 20,000 microcuries. We realize that the estimated size of the thyroid is inaccurate, but we have reason to believe that a greater variable is the response of

TABLE 2. BASAL METABOLIC RATE OF PATIENTS BEFORE AND AFTER TREATMENT WITH RADIOIODINE

Basal metabolic rate, per cent	Patients	
	Before treatment	After treatment
+59 to +50	4	
+49 to +40	12	1
+39 to +30	12	1
+29 to +20	6	1
+19 to +10	6	8
+ 9 to 0		9
− 1 to −10		11
−11 to −20		4
−21 to −30		5

different thyroid glands to the same dosage of radiation. The average dose estimated to have been collected by the thyroid glands in those patients whose results were classified as good was 242 microcuries per gram of estimated thyroid tissue. This figure was based on the data concerning the urinary excretion of the therapeutic dose and because of this, may be 10 to 20 per cent too high. The error due to inability to estimate the weight of the thyroid gland is of greater magnitude. Effective doses in this group ranged from approximately 88 to 574 microcuries collected per estimated gram of thyroid. The 8 patients in this series who had myxedema were

TABLE 3. WEIGHT OF THYROID BEFORE AND AFTER TREATMENT WITH RADIOIODINE

Weight, grams	Patients	
	Before treatment	After treatment
59 to 50	3	1
49 to 40	8	
39 to 30	7	2
29 to 20	13	4
19 to 10	9	9
9 to 0		2
Palpable		7
Not palpable		14
Not known		1

given 158, 168, 201, 252, 272, 321, 366 and 522 microcuries per gram of thyroid tissue and those who had recurrences of exophthalmic goiter were given 110, 182 and 200 microcuries per gram respectively.

Of the 8 patients who were helped but whose conditions were not controlled by the first dose and who were given a second therapeutic dose of I^{131} the first dose averaged 239 microcuries per gram with a range of 91 to 494 microcuries per gram of thyroid tissue. Second doses averaged 111 microcuries per gram and were followed by good control in 4 cases. In 1 case a third dose of 160 microcuries per gram brought about complete control. The sixth patient received the second dose too recently for the result to be known and the result for the other 2 patients is unknown. The average dose per gram of thyroid tissue in those patients who obtained fair results from a single dose was slightly less than that for those who obtained good results.

The average dose of I^{131} given to the 5 patients who had poor results was approximately 151 microcuries per estimated gram of thyroid tissue. These doses ranged from 65 to 224 microcuries per gram. In 1 patient who

received 162 microcuries per gram, a second dose of 53 microcuries per gram produced fair results. The patient who received 65 microcuries per gram for her first dose received 54 microcuries per gram for her second dose; no definite benefit resulted from either dose. It is to be noted here, too, that the average dose per gram of thyroid tissue given to patients who had poor results was still less than that for patients who obtained a fair result.

REACTIONS

No serious reactions were noted by any of the patients we have treated with I^{131}. One patient had a mild febrile reaction associated with nausea for four days; this began two days after the therapeutic dose was administered. His basal metabolic rate rose from plus 46 to plus 62 per cent. It was not possible to say whether he had mild radiation sickness or a mild hyperthyroid reaction or both. The leukocyte count decreased to 3,800 per cubic millimeter during the reaction but rapidly returned to normal.

It was common for the thyroid gland to become hard and slightly tender a few days to a week after a therapeutic dose and for the basal metabolic rate to rise slightly above pretreatment levels for a few days. Slight increases in the sedimentation rate of the blood were noted in some instances but not in others. No changes in renal function were noted, but extensive studies of this factor were not made.

It is impossible to determine at this time whether late reactions of any type may occur. The possibility of genetic effects is a risk which must be accepted by those who are to receive I^{131} therapy. Most of our patients were beyond the reproductive period, but one of the younger ones has become pregnant since receiving I^{131}.

COMMENT AND CONCLUSIONS

It is far too early in our experiences with the therapeutic use of I^{131} to draw definite conclusions. We have been particularly interested in this form of treatment in the small but important group of cases in which serious complications are due either to prolonged hyperthyroidism or to associated diseases and in those in which exophthalmic goiter tends to recur repeatedly after either surgical treatment or treatment with antithyroid drugs. The latter group represents a severe and persistent form of the disease and presumably one which might well present unusual difficulty in its control. Surgical treatment in this group carries a high risk.

The ability of radioiodine to control severe exophthalmic goiter, at least temporarily, seems definite. Further knowledge of dosage is important, and the means which we have used to determine it seem to allow as close an evaluation as any so far devised. Those patients who obtained good results from a single dose received an average dose of 242 microcuries per

gram of thyroid tissue; those who obtained fair results, 239 microcuries per gram; and those who had poor results, 151 microcuries per gram. It would seem, therefore, that an average dose of more than 200 microcuries per gram of thyroid tissue should be tried in cases in which an attempt is made to control the disease with a single dose and it is apparent that some patients treated this way will need a second dose of I^{131} to control the disease. Some patients have needed much less than 200 microcuries per gram of thyroid tissue and doses considerably larger have failed to bring the disease of others under control. This suggests that there may be great individual variability in the sensitivity of different thyroid glands to radiation. The incidence of both myxedema and of recurrence of exophthalmic goiter after treatment is much higher among our patients treated with I^{131} than among patients treated surgically (10, 11). Much more experience is needed before we can have confidence in the accuracy of estimated doses. Immediate reactions to treatment with I^{131} have been inconsequential in our cases thus far.

Of 40 patients with exophthalmic goiter treated with a single dose of I^{131}, 27 obtained good results, 8, fair results, and 5, poor results from a single dose.

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THE EFFECT OF TOTAL THYROIDECTOMY ON THE FUNCTION OF METASTATIC THYROID CANCER*†

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SEVERAL investigators have reported that treatment with radioactive iodine is not only an effective form of therapy in controlling the thyrotoxicosis of Graves' disease but that such treatment may cause the goiters of this malady to disappear. Chapman and Evans (1) have demonstrated that such treatment results in a destruction of thyroid tissue.

Such effects of this form of irradiation on the thyroids of hyperfunctioning hyperplastic goiters have led many clinicians to ask if this form of treatment might be beneficial in cancer of the thyroid. Unfortunately most cancers of the thyroid have little or no function and are incapable of concentrating iodine.

Seidlin, Marinelli and Oshry (2) have had the rare opportunity to study a patient having hyperthyroidism which arose from a widely metastasized hyperfunctioning cancer of the thyroid. Radioiodine administered to their patient was retained by all of the known metastases in concentrations great enough to warrant administering this isotope in therapeutic doses. However, as will be seen from several reported studies, this is an unusual situation.

Graham (3) reported in 1916 that the iodine content of malignant tumors of the thyroid was extremely low even after administering iodine, and that feeding such tissues to tadpoles resulted in no increased rate of metamorphosis.

Since the advent of radioactive isotopes of iodine, several investigators have compared the capacity of tumor tissue with that of normal thyroid

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tissue to concentrate radioactive iodine. Hamilton, Soley and Eichorn (4) were the first to study the distribution of radioactive iodine in normal and cancerous thyroid tissue. With autoradiographic technics they observed that practically none of the iodine was deposited in cancerous tissue and that the iodine collected by normal thyroid tissue was deposited in the colloid. Frantz, Ball, Keston, and Palmer (5) studied three patients having distant metastases from cancer of the thyroid. They observed that one metastasis of one of these patients concentrated an appreciable amount of labelled iodine. Marinelli, Foote, Hill and Hocker (6) who used autoradiographic technics investigated the capacity of certain selected cancers of the thyroid to concentrate radioactive iodine. They observed that 10 of 19 selected cancers possessed the function of concentrating radioactive iodine. Five of the functioning tumors were so-called "benign metastasizing struma." The remaining five tumors which possessed this function had the structure of follicular adenocarcinoma in some portion of the material studied. They failed to demonstrate this function in papillary adenocarcinoma, Hürthle cell adenocarcinoma or in the more anaplastic adenocarcinoma. They concluded that pickup of the iodine is closely linked with certain structural qualities which include an orderly cell arrangement in a follicular pattern and the presence of colloid.

As was pointed out by us at the 1947 meeting (7) of this organization, our experience has also been that malignant tumors of the thyroid possess comparatively little or no function as measured by their capacity to concentrate radioactive iodine. Such observations are not encouraging to those interested in treating cancer of the thyroid with radioactive iodine. However, by removing the normal thyroid we have been able to alter this situation in certain patients having distant nonfunctioning metastatic cancers of the thyroid.

In 1937, Dr. J. H. Means in his monograph on the "Thyroid and Its Diseases" (8) in discussing the function of thyroid cancer wrote the following: "So-called benign metastases with structure identical to normal thyroid tissue must be capable of making hormone. There is no evidence that they do beyond the needs of the body. An interesting experiment, . . . would be to note the effect in an individual with such a metastasis of removing, not the metastasis, but the whole parent thyroid. Under these circumstances would the metastasis form sufficient hormone to prevent myxedema?" By trying this experiment which was suggested more than ten years ago by Dr. Means, in 8 out of 21 patients having nonfunctioning or poorly functioning metastases which had arisen from primary cancers of the thyroid, we have been able to cause the metastases to assume this iodine-collecting and concentrating function of the normal thyroid (Table 1).

TABLE 1

Case	Unit #	Pathologic diagnosis	Thyroidectomy and date		Collection of radioactive iodine before thyroidectomy			Collection of radioactive iodine by metastases after thyroidectomy	Time interval between thyroidectomy and change in function of metastases: or to last unsuccessful measurement	Remarks
			Surgical	Radioactive iodine	Normal thyroid	Primary tumor	Metastases			
				(millicuries)						
Mrs. I.	M.G.H. 481114	Follicular adenocarcinoma	3/ 6/45		1.8%/Gm.§	0.03%/Gm.	73% of dose	27% of dose	32 months	Patient did not develop myxedema.
Mr. B.	M.G.H. 84196	Follicular adenocarcinoma	10/ 8/45				28% of dose	57% *83%	12 months: 15 months	All figures based on excreted radioiodine.
Mrs. R.	M.G.H. 558898	Solid adenocarcinoma		1/16/47 40 mc.	7.4%/Gm.	0.017%/Gm.	0.106%/Gm.	0.0012%/Gm.	4 months	Patient died; necropsy revealed widespread visceral metastases; one lesion only contained radioiodine.
Mrs. C.	M.G.H. 561367	Giant cell carcinoma	1/15/47				0.00	0.00	5 months	Total thyroidectomy done at Lahey Clinic. Dead.
Mrs. L.	M.G.H. 365865	Papillary adenocarcinoma		11/18/47 90 mc.			0.00	0.00	7 months	Patient with myxedema, being followed for subsequent change.
Mrs. L.	M.G.H. 587606	Papillary adenocarcinoma	9/24/47		1.3%/Gm.	0.00	0.00	0.00	6 months	Dead.
Mrs. W.	M.G.H. 577751	Giant cell carcinoma	6/28/47		0.65%/Gm.	0.0024	0.00			Died 1 month later.
Mrs. S.	M.G.H. 594934	Solid adenocarcinoma	11/ 3/47		4.5%/Gm.	0.00	0.00	†0.029[1], †0.420,[2] †0.111[3]	3 months: 3 months and 8 days treatment with TSH	
Mr. H.	Memorial Hospital 82324	Follicular adenocarcinoma		9/14/47 39 mc.	61% of dose		2.1% of dose	23%	100 days	Patient being treated with I^{131}.
Mrs. S.	Memorial Hospital 84479	Follicular adenocarcinoma		2/20/47 61 mc.	25% of dose		2.3% of dose	8.4% of dose	30 days	Patient being treated with I^{131}.

TABLE 1—(*continued*)

Case	Unit #	Pathologic diagnosis	Thyroidectomy and date		Collection of radioactive iodine before thyroidectomy			Collection of radioactive iodine by metastases after thyroidectomy	Time interval between thyroidectomy and change in function of metastases: or to last unsuccessful measurement	Remarks
			Surgical	Radioactive iodine	Normal thyroid	Primary tumor	Metastases			
				(millicuries)						
Mrs. A.	Memorial Hospital 86047	Follicular adenocarcinoma		7/16/47	12% of dose		‡0.92	‡9.1	2 months	
Mrs. M.	Memorial Hospital 84975	Solid adenocarcinoma		4/ 3/47 62 mc.	16.3% of dose		0.00	0.00	3 months	Dead.
Mrs. S.	Memorial Hospital 84497	Giant cell carcinoma		2/20/47	28.0% of dose		0.00	0.00	1 month	Dead.
Mr. A.	Memorial Hospital 85121	Papillary adenocarcinoma	4/ 7/47				0.00	0.00	2½ months	
Mr. Mc.	Memorial Hospital 87060	Follicular adenocarcinoma		9/19/47 25 mc.	16% of dose		0.00	40% of dose	8 months	Pulmonary metastases.
Miss Y.	Memorial Hospital 88506	Follicular and solid adenocarcinoma		1/26/48	3% of dose		0.00	0.00	2	Had radical thyroidectomy before treatment with I^{131}. Being followed for subsequent change.
Miss K.	Memorial Hospital 89431	Follicular and papillary adenocarcinoma		3/ 7/48 75 mc.	15% of dose		0.00			Awaiting change in function.
Miss. M.	Memorial Hospital 89770	Papillary and follicular adenocarcinoma		4/14/48 75 mc.	30% of dose		0.00			Being followed for change in function.
Mr. M.	Memorial Hospital 88040	Hürthle cell adenocarcinoma		12/14/47 40 mc.	17% of dose		0.00	0.00	4 months	Developed myxedema.
Mr. P.	Memorial Hospital 88993	Follicular and solid adenocarcinoma		3/17/48	29.9% of dose		0.00	5%	3 months	Awaiting therapeutic dose.
Mrs. G.	Memorial Hospital 84972	Follicular adenocarcinoma		3/22/47	32.0% of dose		‡0.008	‡0.026	4 months	

§ Per cent of administered radioactive iodine collected per gram of tissue.
* After stopping administration of thiouracil which had produced myxedema.
† Surface counts per minute/microcuries of I^{131} administered. 1) 95 hours after administration of I^{131}. 2) 72 hours after administration of I^{131}. 3) 105 hours after administration of I^{131}.
‡ Surface counts per minute/microcuries of I^{131} retained.

Mrs. T. I., M. G. H. #48114, aged 43: was the first patient in whom this experiment was tried. She was admitted to the Massachusetts General Hospital on February 28, 1945, complaining of a soft tissue mass in the skull and of regrowth of a goiter. The diagnosis was metastatic adenocarcinoma. She gave a history of having had surgical removal in 1933 of a thyroid nodule which had existed for five years. She reported that one year before admission to this clinic she had first noted a lump over the occiput, and that six months before admission she had noted an extensive regrowth of her goiter. She was found to have a lemon-sized, moderately firm mass in the left occipitoparietal area measuring about 5×6 cm. in diameter and raised about 2 cm. above the rest of the skull. She was also found to have a walnut-sized, hard mass in the upper pole of the right lobe of the thyroid. Several large firm lymph nodes were palpable in the right anterior cervical chain. Clinically she was euthyroid and her basal metabolic rate was minus 12 per cent. X-ray studies of the chest and skeleton revealed only an osteolytic defect in the left parietal bone consistent with destruction by metastatic disease. Tracer studies done with radioactive iodine revealed that the occipital metastasis was capable of concentrating only minimal amounts of iodine. It was reasoned that removal of her normal thyroid might be followed by a significant pickup of iodine by the skull metastasis. On March 6, 1945, Dr. R. R. Linton did a total thyroidectomy and a right radical neck dissection. At the same time a biopsy specimen was removed from the metastatic lesion in the skull. The thyroid showed a follicular adenocarcinoma. A similar picture was found in the skull metastasis though this lesion showed more differentiation than the primary lesion and contained some colloid filled acini (Fig. 1). Her normal thyroid was found to have collected 1.8 per cent of the preoperatively administered radioactive iodine per gram of

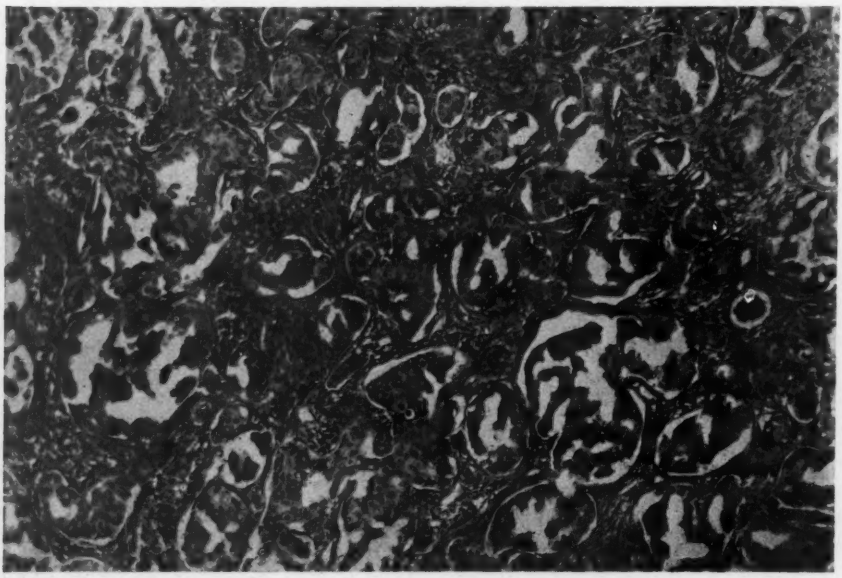

FIG. 1. Biopsy specimen, removed at time of total thyroidectomy, from skull metastasis of Mrs. T. I., M.G.H. #481114. ×160.

tissue. The skull metastasis was found to have collected only 0.06 per cent of the administered radioiodine per gram of tissue. On March 27, another tracer dose of radioactive iodine was administered and *in vivo* measurements over the metastatic lesion were made. Though the patient was found to concentrate less than 3 per cent of administered iodine in the skull metastasis, she did not develop myxedema in a period of four months. Indeed, in July, 1945, her basal metabolic rate was plus 4 per cent. Having the erroneous impression that thyroidectomy was ineffective in altering the function of this tumor, it was decided to attempt removal of the skull metastasis. On July 6, Dr. Mixter made this attempt. However, it was impossible to do more than a partial removal of the tumor. Postoperatively the patient was treated with x-ray and received 1550 roentgens delivered in six doses through a 10 × 10 field. The patient returned to her home in Rochester, New York, and was not seen again until July of 1947. At that time she was taking desiccated thyroid in a daily dose of 65 mg. (1 grain). She reported that in April of 1947 she had noted a regrowth of the tumor in her occipitoparietal area. She was found to have regrowth of a moderately firm tumor, which measured about 2 cm. in diameter, at the site of the previous occipital tumor. She had a basal metabolic rate of minus 16 per cent. A tracer dose of radioactive iodine was given on July 3, of which she excreted 92 per cent in the urine. *In vivo* measurements revealed radioactivity in the skull lesion and in the neck. There was about three times as much activity in the skull metastasis as in the neck. On August 1, she was advised to stop taking thyroid. She was readmitted to the hospital in October of 1947 and was found to have a B.M.R. of minus 11 per cent. Studies revealed an increase in size of the occipital lesion and a new osteolytic lesion in the third dorsal vertebral body. A tracer dose of radioactive iodine was administered on October 6. Of this tracer dose, she excreted only 48 per cent. By *in vivo* measurements, it was estimated that she concentrated 30 per cent of the administered dose in her occipital lesion, 10 per cent in the region of her thyroid and 10 per cent in the vertebral lesion (Fig. 2). This patient is now being treated with large doses of radioactive iodine.

The study done in this first patient was at first thought to be a failure because immediately following removal of the thyroid we were unable to demonstrate change in the function of her metastatic lesion. The fact that she had not developed myxedema four months after removal of her normal thyroid would indicate that her metastasis was manufacturing amounts of thyroid hormone adequate to maintain her in a euthyroid state. In the light of present knowledge it is unfortunate that we were unable or too short sighted to follow through on this study in 1945.

Mr. B., M.G.H. #84196, aged 60, was the first patient in whom we successfully completed this observation. He was admitted to the wards of the Massachusetts General Hospital in August of 1945, complaining of a severe back pain. He was found to have a metastatic tumor involving the first and second lumbar vertebral bodies. At operation a biopsy specimen of the tumor was taken and the spine was fused. The biopsy specimen revealed a follicular adenocarcinoma with some alveolar structure resembling thyroid tissue (Fig. 3). In October of 1945, tracer studies with radioactive iodine were done and *in vivo* measurements were made for radioactivity. Because of the depth of the tumor and the inadequacies of our counting equipment, we were unable to quantitate the radioac-

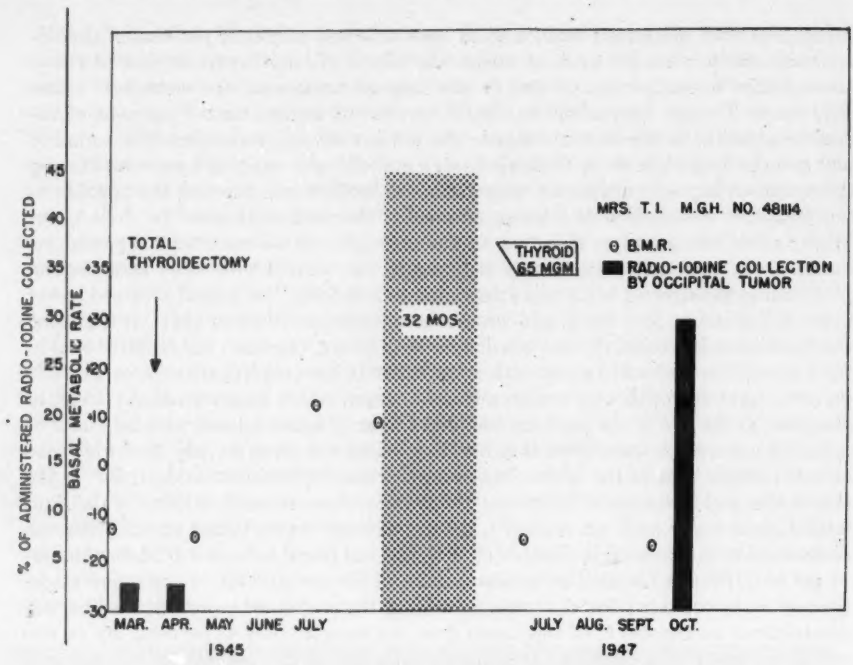

FIG. 2. Mrs. T. I., M.G.H. #481114. Illustrating basal metabolic rate levels and radio-iodine collections of metastatic tumor before and after removal of normal thyroid.

tivity in his metastatic tumor. However, measurable radioactivity was detected over the vertebral metastases. Again it was reasoned that we might be able to increase the avidity of this tumor for radioactive iodine by removing the normal thyroid. On October 8, 1945, a total thyroidectomy was done by Dr. Oliver Cope. The thyroid was found to contain a solid malignant adenoma. Fifty days after removal of the thyroid, the patient showed no evidence of myxedema and was excreting only 70 per cent of a tracer dose of radio iodine. By *in vivo* measurements, he was concentrating radio iodine in the metastases only. At this time we decided to treat him with thyroid-stimulating hormone in an attempt to increase the avidity of his tumor for radioactive iodine. He received thyroid-stimulating hormone 100 (guinea pig) units daily for eight days. We observed an increase in his serum protein-bound iodine and a decrease in urinary excretion of radio iodine to 40 per cent. After fifteen months this patient still showed no evidence of myxedema and he still was excreting in the neighborhood of 40 per cent of the radio iodine (Fig. 4a) Thus it appeared that in the absence of his normal thyroid the tumor was utilizing iodine in a physiologic manner.

Next it was decided to study the effect of thiouracil on the function and growth of the tumor. The drug was administered in a dose of 0.2 Gm. every eight hours for 106 days. The patient did develop myxedema as evidenced by a classical clinical picture and a fall in the basal metabolic rate and serum protein-bound iodine to myxedematous levels. By x-ray examination the tumor was found to have increased in size during the period

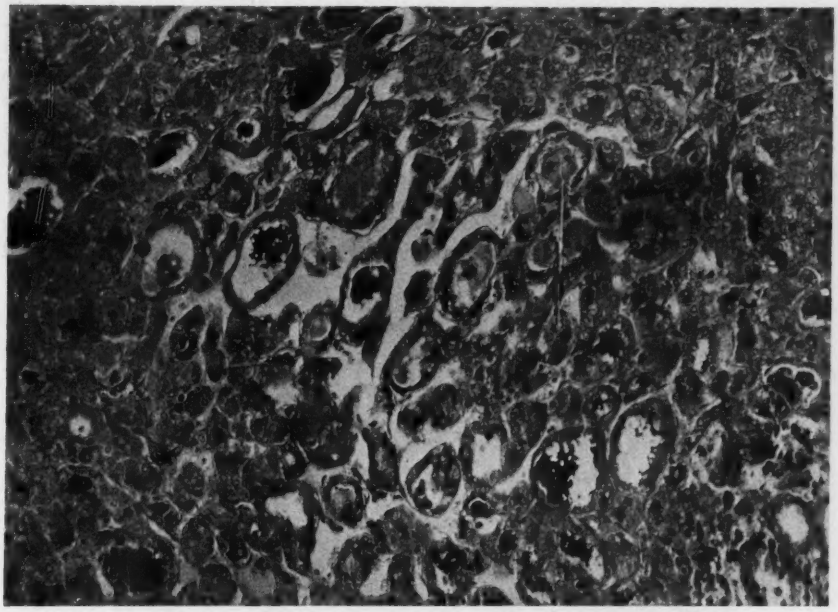

FIG. 3. Biopsy specimen, removed before total thyroidectomy, from vertebral metastasis of Mr. B., M.G.H. #84196. ×160.

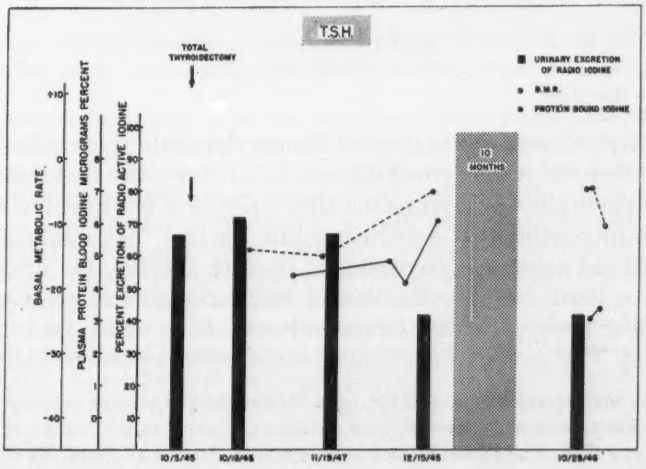

FIG. 4. (a) Mr. B., M.G.H. #84196. Illustrating basal metabolic rates, blood protein-bound iodines and urinary radioiodine excretions before and after thyroidectomy and after treatment with thyroid-stimulating hormone.

of treatment with thiouracil. We were surprised to observe that even though he did develop myxedema, he excreted only 60 per cent of an administered tracer dose of radioiodine and concentrated a significant amount of radioiodine in the tumor, in spite of the fact that he was taking thiouracil in doses great enough to produce a very effective block to the concentration of iodine in the usual case of Graves' disease. Seventy-two hours after stopping administration of thiouracil another tracer dose of radioiodine was administered. Only 15 per cent of this dose was excreted in the urine (Fig. 4b).

Thus this patient's metastasis, which had measurable function before thyroidectomy, developed an even greater degree of function and provided

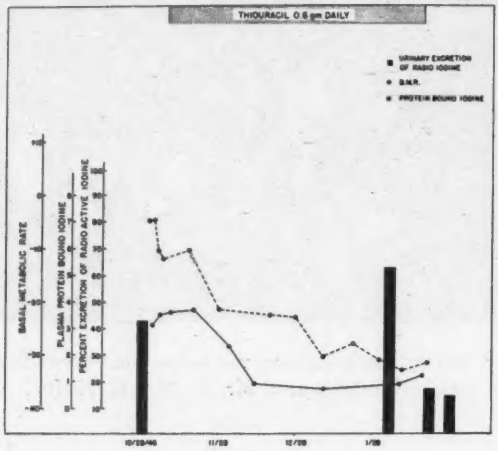

FIG. 4. (b) Mr. B., M.G.H. #84196. Illustrating basal metabolic rates, blood protein-bound iodines and urinary excretion of radioactive iodine before, during and after treatment with thiouracil.

enough thyroid hormone to prevent the development of myxedema following total removal of the normal thyroid. It is noteworthy that this patient's tumor became more avid for iodine after a period of treatment with thiouracil. It is interesting that notwithstanding the fact that administration of thiouracil did cause a myxedematous state to develop, the drug did not produce a block to the utilization of iodine comparable to that usually observed in patients having Graves' disease, when under the influence of this agent. This patient is now being treated with radioactive iodine.

Mr. H , Memorial Hospital # 82324, aged 74, was the first patient in whom we tried to alter the function of metastatic thyroid cancer by destroying the normal thyroid with radioactive iodine. He entered Memorial Hospital on August 17, 1946. He was found to have a primary solid adenocarcinoma of the thyroid with metastases to the right ileum (Fig. 5). Tracer studies with *in vivo* measurements revealed that he concentrated 61 per cent of the administered radioiodine in the thyroid and 1.2 per cent in the metastatic lesion. Because this patient refused to have a surgical thyroidectomy, his normal thyroid

was destroyed by a 39-millicurie dose of I^{131} administered on September 14, 1946. One hundred days later he was found to collect 2.1 per cent of a tracer dose of radioactive iodine in the thyroid and 23 per cent of the dose in the metastatic tumor (Fig. 6). This patient is also being treated with radioactive iodine.

Mrs. S., M.G.H. # 594934, aged 41, illustrates the effect of thyroid-stimulating hormone on the iodine collection of a nonfunctioning metastasis in a totally thyroidectomized patient. This patient entered the Massachusetts General Hospital on the neurosurgical service on October 18, 1947, complaining of severe bilateral leg pain of six

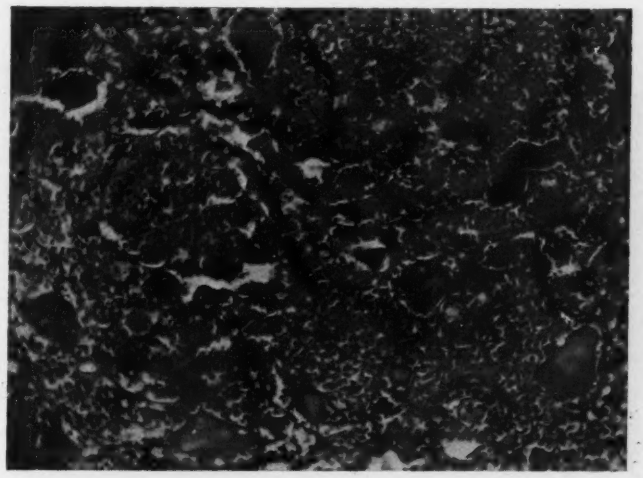

FIG. 5. Biopsy specimen removed from primary tumor of Mr. H., Memorial Hospital #82324. ×100.

months' duration. She was found to have tenderness over the lumbosacral area, more on the right side than on the left. She presented a hard, nontender mass, 4 cm. in diameter, in the left lobe of the thyroid. Clinically she was euthyroid with a B.M.R. of plus 11 per cent. X-ray studies revealed a large, irregular osteolytic lesion in the sacrum and another similar area of destruction in the wing of the right ileum, consistent with metastatic disease. Biopsy of this tumor revealed a solid adenocarcinoma consistent with a primary thyroid or breast cancer (Fig. 7). A tracer dose of I^{131} was administered, following which she was found by *in vivo* measurements to concentrate none of the radio iodine in her metastatic lesion. Being unable to demonstrate any evidence of breast, renal or gastrointestinal cancer and finding the discrete nodule in her thyroid, it was decided that the primary cancer was probably in the thyroid and that the thyroid should be totally removed. This was done on November 3 by Dr. Oliver Cope. The nodule in the thyroid was found to be a hyperplastic adenoma without evidence of malignancy. With the usual routine studies, no primary cancer was found in the thyroid. The patient was allowed to develop myxedema. On February 5, 1948, she was found to have a B.M.R. of minus 29 per cent and a serum protein-bound iodine of 0.7 microgram per cent. A 2-millicurie tracer dose of I^{131} was administered at this time. By *in vivo* measurements she was found to have only 58 surface counts per minute over the sacral tumor ninety-five hours after

administering the iodine. By dividing the surface counts per minute by the microcuries of radioiodine administered we obtained a ratio of 0.029. The patient then received 30 mg. daily of Armour's thyrotropic hormone (3.5 chick units per milligram) for eight days, in an attempt to test the possibility of inducing function in this tumor by maximal stimulation. Twenty-four hours after the last injection of T.S.H. she received another 2-millicurie dose of I^{131}. Seventy-five hours later she was found to have 839 surface counts per minute over the sacral lesion and at 124 hours, she had 222 surface counts per minute, giving ratios of 0.420 and 0.111 (Fig. 8).

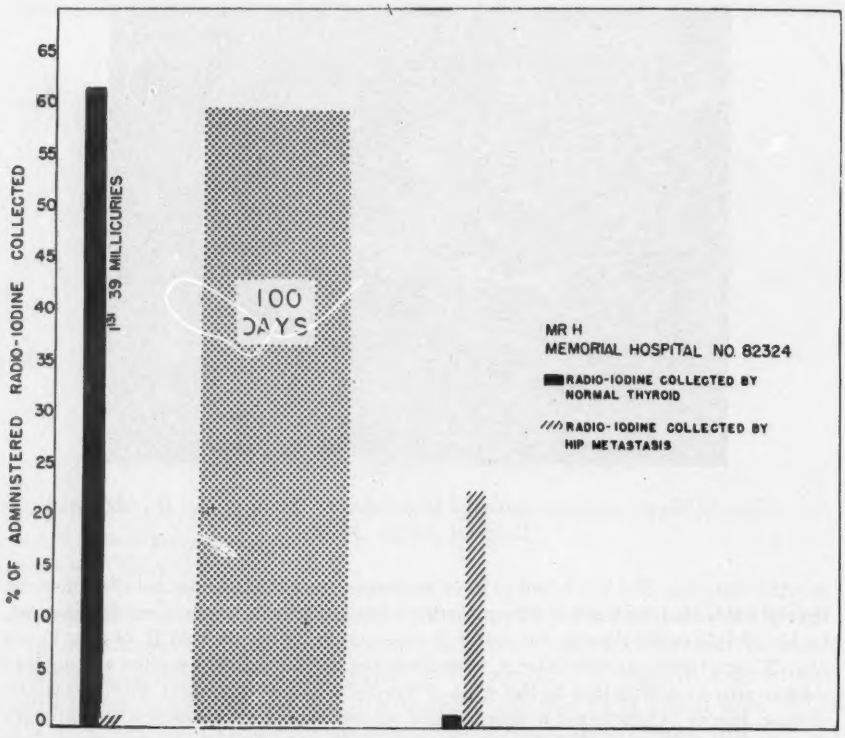

FIG. 6. Mr. H., Memorial Hospital #82324. Illustrating radioiodine collection by normal thyroid and by metastatic lesion in hip before and after destroying normal thyroid by administration of large dose of I^{131}.

Thus by administering T.S.H. to this thyroidectomized myxedematous patient whose metastatic tumor had not assumed any function we were able to cause the tumor to collect significant amounts of radioiodine. It is interesting also that by this means we were able to provide evidence that this metastatic tumor arose from the thyroid.

Although in 8 cases removal of the normal thyroid has resulted in the metastases assuming enough iodine-concentrating ability to warrant instituting a program of therapy with radioactive iodine, in a number of cases this form of treatment has not been effective. The case history of one of our failures follows:

Mrs. C. L., M.G.H. # 587606, a 73-year-old white female was admitted to the wards of the Massachusetts General Hospital on September 14, 1947, complaining of a tumor in the neck. She gave a history of having been in good health until six weeks before admission when, following a sore throat, she first noted a painless swelling in the left side

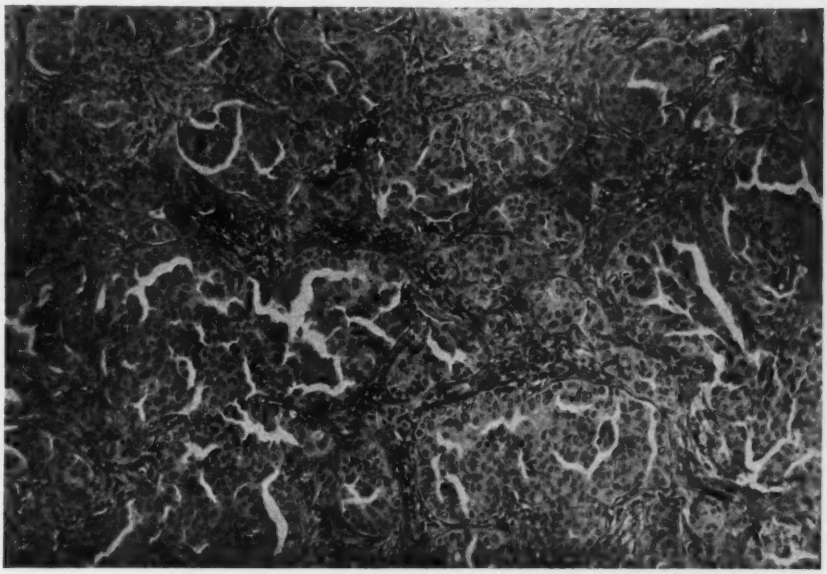

FIG. 7. Biopsy specimen, removed before total thyroidectomy, from metastatic lesion in the sacrum of Mrs. S., M.G.H. #594934. ×160.

of her neck. On physical examination she was found to have a large firm-to-hard mass in the left lobe of her thyroid with several hard nontender enlarged lymph nodes in the left anterior cervical chain which seemed to be matted together. There were no distant metastases. She was found to have a B.M.R. level of plus 3 per cent. On September 24, Dr. E. Hamlin did a total thyroidectomy. Because of the fact that at operation diseased lymph nodes were found to extend deep into the mediastinum, a neck dissection was not done. The tumor was found to be a papillary adenocarcinoma (Fig. 9). Of a tracer dose of radioiodine given before operation, she was found to concentrate 1.32 per cent of the administered iodine, per gram of normal thyroid tissue. No radioactivity whatever was concentrated in the tumor. By October 23 this patient had developed myxedema with a B.M.R. of minus 22 per cent and a protein-bound blood iodine of 0.7 micrograms per

100 cc. A tracer dose of radioactive iodine given at this time revealed no iodine collection. By March 30, this patient had developed a profound myxedema. Of a tracer dose of radioactive iodine administered at this time none was concentrated in the tumor (Fig. 10). This failure to respond could possibly be related to x-radiation that she had received postoperatively. However, it is of interest to point out that the papillary adenocarcinomas have uniformly shown practically no capacity to concentrate radioactive iodine. Thus far we have been unable to alter this state of nonfunction in any metastatic papillary adenocarcinoma.

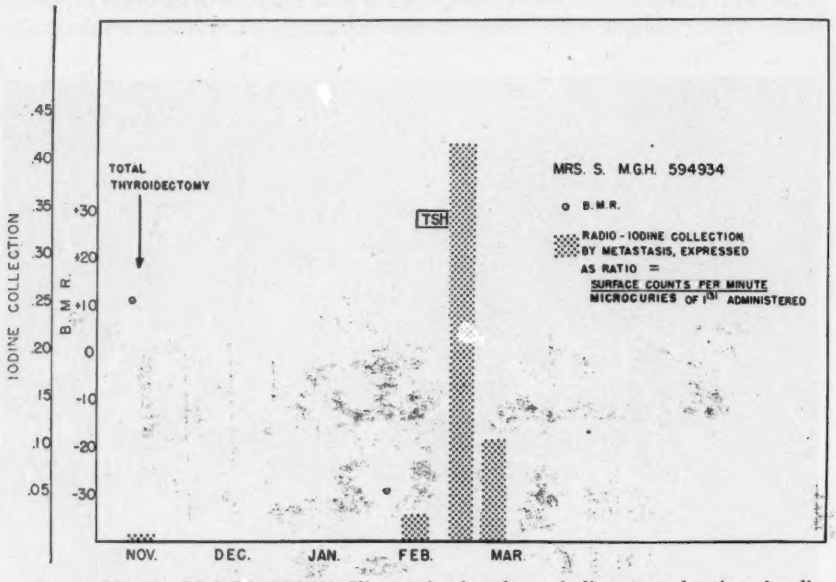

FIG. 8. Mrs. S., M.G.H. #594934. Illustrating basal metabolic rate and ratios of radioiodine collection before and after total thyroidectomy and after treatment with thyroid-stimulating hormone.

DISCUSSION

The normal thyroid has been removed or destroyed in 21 patients who had nonfunctioning cancerous metastases of thyroid origin. In 7 cases the normal thyroid was removed surgically; in 14 cases the remaining normal thyroid was destroyed by large doses of radioactive iodine, I^{131}. In 5 cases death occurred within six months of the time that the thyroid was removed or destroyed. One of these patients was found at necropsy to have widespread metastases. Only one of these metastases concentrated a significant amount of radioiodine. Yet by measurement, the amount of radioactivity concentrated in this single lesion was not as great as that demonstrated in the primary tumor which had been removed four months earlier. In 8 patients there was observed a significant increase in the collection of iodine

by the metastatic lesions which previous to thyroidectomy had shown minimal to no function. In all of our successful cases the type of tumor was adenocarcinoma or follicular adenocarcinoma. In one patient whose metastatic lesion showed the structure of a solid adenocarcinoma, we were unable to demonstrate any function of the metastasis ninety-six days after total removal of the thyroid. However, after administering thyroid-stimu-

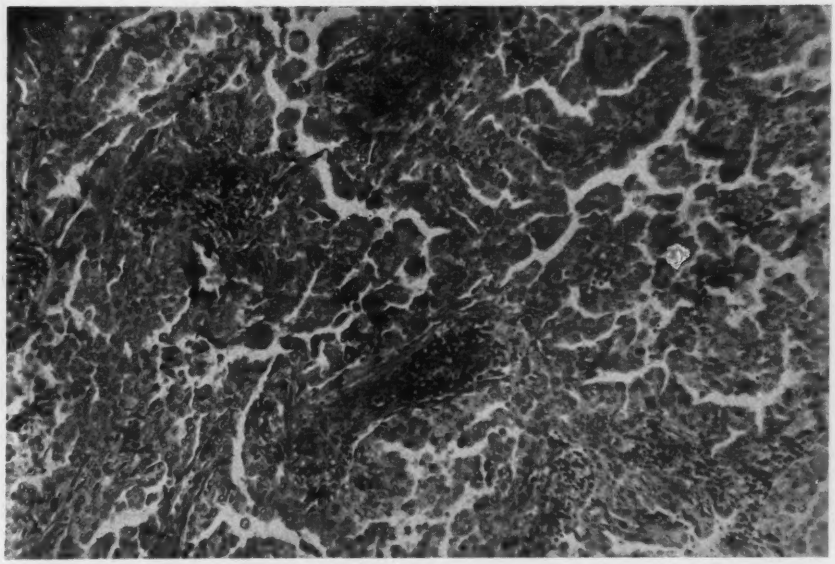

FIG. 9. Primary tumor removed at time of total thyroidectomy, Mrs. C. L., M.G.H. #587606. ×160.

lating hormone for eight days, there was demonstrated a significant pickup of radioactive iodine by the tumor. We have attempted to induce iodine collection by nonfunctioning metastatic tumors arising from papillary adenocarcinomas in 4 cases. In no instance have we as yet been able to alter the function of such tumors. This procedure has been attempted in 3 patients who had metastases from giant cell carcinoma of the thyroid. In all of these cases death occurred before we were able to produce any change in the function of the metastasis. There are 4 patients with metastatic adenocarcinoma of the thyroid who have been treated in the last four months and are now being followed.

The mechanisms by which these changes occur in the function of certain metastatic lesions from cancer of the thyroid are not known. However, it is quite obvious that certain nonfunctioning cancers of the thyroid do

respond to the organism's need for thyroid hormone, by assuming the function of its parent organ. From our observations in one patient whose tumor assumed the function of concentrating iodine following the administration of thyroid-stimulating hormone, it would appear that an ample

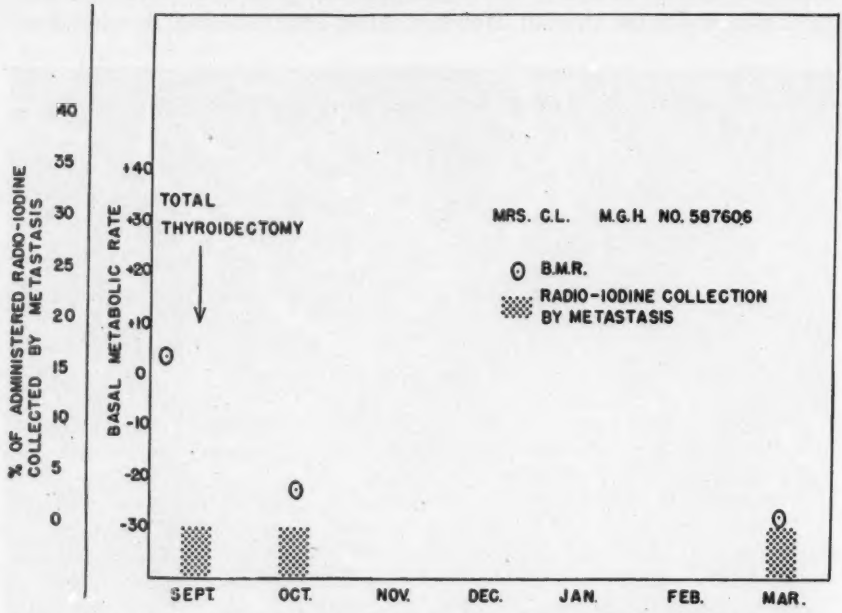

FIG. 10. Mrs. C. L., M.G.H. #587606. Illustrating basal metabolic rates and radioiodine collection by metastases before and after total thyroidectomy.

supply of this pituitary hormone is necessary for this change to take place.

We have been unable to obtain enough material to make any statement as to histologic or structural changes resulting in these tumors following thyroidectomy.

CONCLUSIONS

1. The normal thyroid has been removed surgically or destroyed by large doses of radioactive iodine in 21 patients having relative or absolute nonfunctioning metastatic thyroid cancer. Among these 21 cases, there were 4 papillary adenocarcinomas, 13 solid and/or follicular adenocarcinomas, 3 giant cell carcinomas and 1 Hürthle cell adenocarcinoma.

2. Eight of the metastatic solid and/or follicular adenocarcinomas assumed the capacity to concentrate radioactive iodine after the normal thyroid was removed. The time required to observe these changes varied between one and thirty-two months. One patient having a solid adenocar-

cinoma, whose metastatic tumor failed to collect iodine even after the development of myxedema, was found to concentrate in her metastatic lesion a significant amount of radioiodine after treatment with thyroid-stimulating hormone.

3. We have failed to demonstrate any iodine-concentrating function of the metastatic lesions in the 4 cases of papillary adenocarcinoma.

4. The 3 patients with giant cell carcinoma died within six months after thyroidectomy and before we were able to demonstrate any change in function of the metastasis.

5. The one patient having metastatic Hürthle cell adenocarcinoma is being followed and has thus far shown no change in function in the metastasis.

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THE RELATIONSHIP OF HYPERTHYROIDISM TO MYASTHENIA GRAVIS*

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MUSCULAR weakness and fatigability may be prominent in uncomplicated hyperthyroidism. The mechanism is not clear but it seems likely that there is direct embarrassment of muscle metabolism. Certainly creatinuria is marked, and muscle isolated from a hyperthyroid animal uses much more oxygen than normal (1). In addition, however, there are a number of well defined neuromuscular disorders which may coexist with hyperthyroidism and which may be modified by it. A study of the interrelationships between these conditions might well shed light upon them, or even more important—upon the manifold problems of muscular fatigue in man.

The following neuromuscular disorders which may appear with the hyperthyroid state are described briefly in order to emphasize the wide variety of mechanisms that may be involved:

1. *Exophthalmic ophthalmoplegia* (2, 3). This consists in progressive protrusion of the eyeballs due to a dystrophic process affecting the extraocular muscles. There is edema, fatty infiltration and swelling of the muscle fibers. This condition is apt to appear or become aggravated when the hyperthyroidism is brought under control. For this reason, and because of numerous experimental facts, the anterior pituitary thyrotropic hormone is suspect, rather than the thyroid itself.

2. *Acute thyrotoxic encephalo-myopathy.* This jawbreaker title covers fairly completely a condition recently described in the Scandinavian literature (4). This results in a picture of bulbar palsy sometimes associated with Parkinson-like tremors and delirium or coma. It is relieved by treatment of the hyperthyroidism.

3. *Chronic thyrotoxic myopathy* (5) is characterized by generalized weakness, wasting and fasciculation of the voluntary muscles. This picture, which resembles so closely the incurable progressive muscular atrophy, vanishes after subtotal thyroidectomy.

4. *Familial periodic paralysis* (6). This rare and fascinating condition is

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really a disorder of potassium metabolism in relation to neuromuscular function. Recurrent attacks of flaccid paralysis occur, lasting many hours and disappearing spontaneously. Attacks are associated with a fall of serum potassium and they are rapidly terminated by administration of potassium salts. These bouts of paralysis are greatly increased in frequency and severity in the presence of hyperthyroidism or with thyroid feeding.

5. *Myasthenia gravis* (7). This challenging disease is characterized by weakness and undue fatigability of the skeletal muscles. Heart and visceral musculature is quite unaffected. The muscles innervated from the brain stem are first, and most, affected. The patient is thus apt to have drooping eyelids, a blank, expressionless appearance, a nasal voice, and difficulty in chewing and swallowing. In severe cases there may be marked weakness and fatigability of the limb muscles so that the arms or legs can scarcely be lifted. In extreme cases the respiratory muscles may become affected and the patient dies of respiratory paralysis or spasm of the larynx.

The above features resemble unmistakably the more acute and evanescent effect of curare poisoning in man, when just the same series of events transpires with increasing doses of the drug.

The general character of myasthenia gravis is suggestive of an endocrine or metabolic disorder. Onset is usually after puberty and in early life. There is a tendency to remissions. Modifications may occur during pregnancy or with changes of thyroid function. At autopsy no structural change is found in the nerves or muscles except for the presence of scattered lymphorrhages, which can scarcely be considered causative. The only other common finding is hyperplasia or tumor formation in the thymus, which occurs in about half the cases according to the somewhat weighted autopsy statistics, and in a lesser but still notable number if exploratory operation is carried out in an unselected series of cases.

There are other similarities, too, between myasthenia gravis and curare poisoning. Numerous electromyographic studies in both conditions indicate that there is a sort of block to normal neuromuscular function. The motor nerve fibers seem to conduct normally, and the response of skeletal muscle to direct stimulation is normal, but the transmitting machinery from motor end plates to muscle does not function properly. Furthermore, both conditions respond dramatically to anticholinesterase drugs such as eserine and prostigmin. The myasthenic patient too, is made very much worse by minute doses of curare.

CASE REPORTS

We report here two cases of coexistent hyperthyroidism and myasthenia gravis, in each of which there was an inverse relationship between the two conditions. They are the only two instances of the combined diseases

that we have been able to find in the records of the Royal Victoria Hospital and the Montreal Neurological Institute. Special attention is drawn to the charts (Figs. 1 and 2). They contain many of the necessary details and the latter are therefore omitted from the case reports. The prodigious amount of detail necessary to complete Figure 2 was kept by the patient

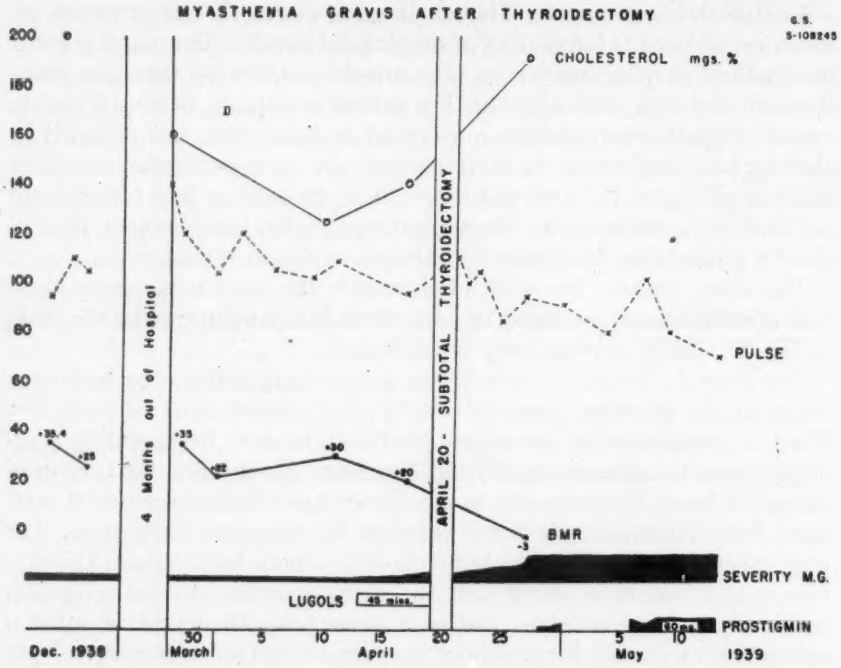

FIG. 1.

herself, a registered nurse, and was put into graphic form by Miss Doris Brophy.

Case 1 (MNI 4200, M 81733, S 108245). In the following case mild symptoms of myasthenia gravis blossomed into the full picture following treatment of the hyperthyroidism:

G. S., female, aged 41, was admitted to the Montreal Neurological Institute in December, 1938. Eighteen months previously, symptoms of hyperthyroidism had appeared with nervousness, heat intolerance, profuse sweating and loss of 40 pounds in weight. These symptoms persisted until the time of admission. Fifteen months before admission, mild and variable symptoms of myasthenia gravis became superadded and there was occasional diplopia, drooping of an eyelid, or transient weakness of hands, jaws or legs. On admission, physical examination showed moist, warm skin, fine tremor of the outstretched hands, and a basal pulse rate of 92–112. Blood pressure was 150/85. There was

bilateral lid lag, diplopia on gazing toward the right and a question of diminished downward gaze, bilaterally. Evidences of myasthenia gravis were minimal. The basal metabolic rate and other relevant laboratory information are shown in Figure 1. The patient was discharged with the understanding that she was to return after Christmas for operation.

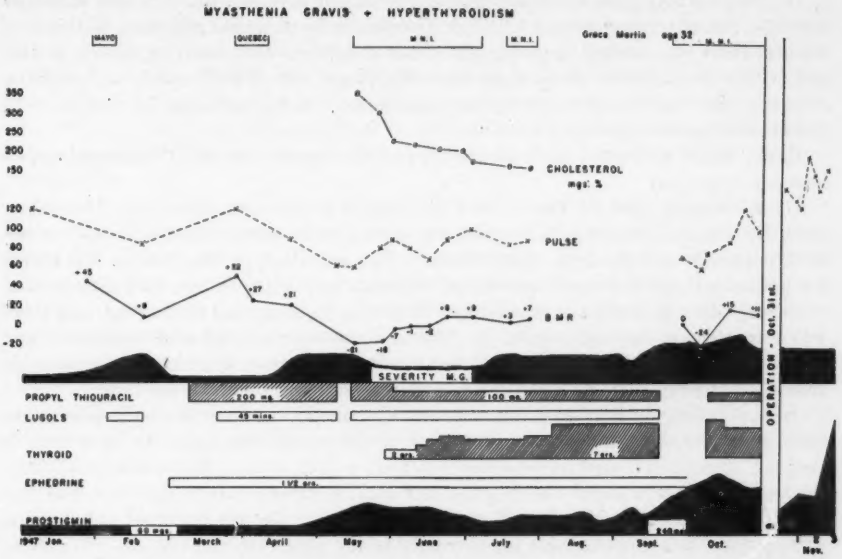

FIG. 2.

She was re-admitted to the metabolism ward in March, 1939. At this time there was marked tremor of the outstretched hands and coarse muscular twitchings involving most of the muscle groups in the body at one time or another. The thyroid was not distinctly palpable except perhaps in the area of the isthmus. There was no bruit, and no obvious enlargement to percussion of the superior mediastinum. There were no signs of myasthenia gravis with the patient at rest.

There was definite creatinuria. On March 30, 24-hour excretion of creatine was 1.02 Gm. and of creatinine 2.25 Gm.; March 31, creatine—0.718, creatinine—0.980. The B.M.R. on March 29 was plus 35 per cent. On April 13 Lugol's solution in a dose of 15 minims three times daily was started, following which there was some improvement in the pulse rate, the average now being 90–100. The B.M.R. on April 17 was plus 20 per cent. On April 20 subtotal thyroidectomy was performed by Dr. Gavin Miller.

The patient made an uneventful recovery and the B.M.R. on April 27 was minus 3 per cent. At about this time it was noticed that she had an attack of numbness about the lips and tongue, with some slurring in speech and some difficulty in swallowing. Neurological findings were essentially normal during that attack. The patient was given 0.5 mg. of prostigmin, which cleared up her symptoms within a few minutes. Serum calcium at this time was normal, and there was no change in serum potassium or serum phosphorus. There was no evidence of carpopedal spasm.

During the next few days she had several attacks of this condition, and on May 6 she was seen to have very marked generalized weakness and there was a nasal tone to her voice. There was weakness of the orbicularis oculi muscles and strabismus, and weakness of the muscles of the mouth with only slight movement of the soft palate. There was weakness of all the extremities, although the deep reflexes were all present.

On May 6 a myogram was taken showing definite myasthenic reaction. She was then given 0.5 mg. of prostigmin and 1/100 gr. atropine by hypodermic injection. Within five minutes there was marked improvement in her condition, with return of muscle power, and within ten minutes the patient was able to get out of bed, speak, and swallow normally. She was then given 15 mg. prostigmin and 1/100 gr. atropine by mouth every 4 hours with good control of symptoms.

Case 2 (MNI 47-14291). In the following case the see-saw balance is illustrated on five separate occasions:

G. M., female, aged 32, first noticed blurring of vision with diplopia in December, 1943. No diagnosis was established. She was given a right opaque lens and carried on her work normally until January, 1946, when she had an attack of "flu." After this illness she noticed a little slurring in speech and difficulty in holding things. Towards the end of the day she began to have increasing difficulty in speaking and in chewing, and there was a drooping of the right eyelid. In February she experimented with prostigmin and experienced immediate improvement. Her condition was then diagnosed as myasthenia gravis. Prostigmin, 30 to 60 mg. per day, continued to give relief for some time.

In June, 1946, she noticed palpitation and dyspnea on exertion. She became nervous, restless and irritable and developed tremor of the hands. She began to have trouble sleeping, developed a marked intolerance to heat, and in spite of an increase in appetite she lost 20 pounds in about two months. Her basal metabolic rate at that time was plus 25 per cent, and a few weeks later it was plus 37 per cent. Despite the onset of hyperthyroidism there was unmistakable improvement of the myasthenic symptoms. No specific treatment was given save rest and sedation (phenobarbital, ½ grain, three times daily), and she resumed her work in August, 1946. She continued doing a full day's work, but with considerable fatigue, until January, 1947, when she went to the Mayo Clinic for investigation. Her clinical symptoms, medication and laboratory findings from that time on are shown graphically in Figure 2. Many other laboratory investigations were carried out but they are noncontributory.

Medication with Lugol's solution for fourteen days resulted in an improvement in the hyperthyroid condition, but there was a concurrent exacerbation of myasthenic symptoms. Cessation of Lugol's therapy brought about an improvement in the myasthenia, but this was accompanied by an increase in pulse rate and the symptoms of hyperthyroidism returned. Lugol's was again prescribed and propylthiouracil was started in March. This again resulted in improvement of the hyperthyroid condition while the myasthenia gravis became worse. At the time of her first admission to the Montreal Neurological Institute she had had marked increase in generalized weakness, difficulty in swallowing, and had fallen down frequently. She also had trouble with fluids regurgitating into the nose, in spite of a substantial increase in prostigmin medication.

The B.M.R. had now dropped so low, as a result of propylthiouracil therapy, that the patient was considered to be hypothyroid. It was thought that it might be possible to administer thyroid in dosage sufficient to improve the myasthenia without causing frank hyperthyroidism. It was also hoped that if there was a pituitary thymotropic hormone, thyroid feeding might inhibit its activity along with that of the thyreotropic

hormone. This attempt to outwit the pituitary was not successful. Thyroid extract was administered, with temporary improvement of the myasthenia gravis. Two weeks after discharge from hospital, however, the patient returned complaining of increased weakness, trembling of the hands and legs and drooping of the left eyelid, despite increased thyroid feeding. The condition was again brought under temporary control with prostigmin and thyroid and she was able to return to part time duty.

In September she began to have difficulty with breathing and increased muscular fatigue despite increased dosage of prostigmin. All other medication was suspended for a time and she was brought into hospital by ambulance in an extremely weakened condition. During this admission her myasthenic symptoms were brought under control with difficulty in spite of resumed thyroid medication and greatly increased prostigmin dosage (see Fig. 2). She was transferred to the surgical division on October 29, 1947, for thymectomy.

Operation was carried out on October 31 by Dr. C. A. McIntosh. The right and left lobes of the thymus were normal in appearance and measured about $3\frac{1}{2}$ inches in length, $\frac{1}{4}$ inch in width and $\frac{3}{8}$ inch in thickness. The pathologic diagnosis was involuted thymus.

The immediate postoperative course was stormy but not unusual. She was placed in a respirator on the third day, which eased her breathing, but there was marked sinus tachycardia—120 to 140 per minute. She died later the same day, death apparently being due to circulatory failure with sudden stoppage of the heart. Autopsy showed hyperemia and edema of the lungs (bilateral); hydrothorax (right: 150 cc. of fluid); atelectasis of the lungs (right upper and left lower lobes); atrophy of the thyroid (10 grams); atrophy of the liver (890 grams); old fibrous adhesions of the pleura (bilateral); and a hemorrhagic cyst of the right ovary.

HYPERTHYROIDISM AND MYASTHENIA GRAVIS

This association is rare but it may be informative. Eaton (8) advises us that 6 per cent of myasthenic patients studied at the Mayo Clinic have shown co-existent hyperthyroidism. The cases available in the literature are few in number. Physicians who have studied the relationship would do a real service by publishing their observations. We have not made an exhaustive search, but we have assembled in Table 1 data from eight cases (including our own two cases) for which adequate information has been reported.

It is of interest that all of these patients have been women and that their ages ranged from 20 to 59 years. Initial basal metabolic rates ranged from plus 21 per cent to plus 52 per cent before any treatment was instituted for the hyperthyroidism. Symptoms and signs of muscle weakness were characteristic of myasthenia gravis and responded in all instances to prostigmin. Of the four instances in which myasthenia gravis appeared before the hyperthyroidism, the later appearance of hyperthyroidism brought unmistakable improvement of the symptoms of myasthenia in two (cases 2 and 8).

For the most part there seems to be an inverse, "see-saw" relationship between the two conditions—the myasthenia waning with the onset of

hyperthyroidism or waxing with the treatment of the hyperthyroidism. This relationship was observed in both of our cases and was illustrated on five occasions in our second case, as follows:

(a) Onset of spontaneous hyperthyroidism—myasthenia gravis improved.
(b) Iodine therapy —myasthenia gravis worse.
(c) Cessation of iodine therapy —myasthenia gravis improved.
(d) Thiouracil therapy —myasthenia gravis worse.
(e) Thyroid feeding —myasthenia gravis improved.

The last of these (e) was an attempt to outwit the anterior pituitary thyrotropic hormone, but it was unsuccessful and the patient died following thymectomy with symptoms which suggested cardiovascular collapse rather than myasthenia gravis.

TABLE 1

Case No.	Age, Yrs.	Sex	First disease to appear	Basal metabolic rate. Per cent	Response to prostigmin	Effect of treatment of hyperthyroidism on course of myasthenia gravis	Author
1	39	F	Hyperthyroidism	+21	Yes	Thyroidectomy—recovered	Kowallis, Haines and Pemberton (9)
2	20	F	Myasthenia gravis	+52	Yes	X-ray—worse	Thorner (10)
3	59	F	Myasthenia gravis	+22	Yes	Iodine—better Thiouracil—? worse	Thorn and Eder (11)
4	50	F	?	+46	Yes	Thyroidectomy—better	Thorn and Eder (11)
5	27	F	Myasthenia gravis	+40	Yes	Iodine—worse Thiouracil—worse Thyroidectomy—worse	Cohen (12)
6	50	F	Hyperthyroidism	—	Yes	Thyroidectomy—recovered	Sheldon and Walker (13)
7	38	F	Hyperthyroidism	+30	Yes	Thyroidectomy—worse	McEachern and Parnell
8	32	F	Myasthenia gravis	+46	Yes	Iodine—worse Thiouracil—worse Thyroid feeding—better	McEachern and Parnell

The "see-saw" relationship did not hold true, however, for three of the eight cases in Table 1, which makes the matter more confusing.

Possible mechanisms

Let us examine the various possible derangements that might occur in the chemical transmitting mechanism from nerve to skeletal muscle in myasthenia gravis. (a) *Deficient synthesis or liberation of acetylcholine at motor end plates.* This is a popular theory and may well be the correct one, but it is difficult to prove or disprove. Further critical experiments with

newer techniques may give the answer one way or another. (b) *Increased breakdown of acetylcholine due to overactivity of the enzyme cholinesterase.* It has been shown by a number of workers that blood cholinesterase is normal in myasthenia gravis. Muscle cholinesterase has also been found normal in the few cases where the determination has been made. (c) *Diminished sensitivity of muscle to acetylcholine.* Here we run into the confusing observation that myasthenic muscle, unlike curarized muscle, is actually hypersensitive to acetylcholine injected into the nutrient artery. This might mean, of course, that the two conditions are quite different in mechanism. On the other hand, curare poisoning is an acute affair whereas myasthenia gravis is chronic. We know that denervation of a muscle results, after a couple of weeks, in increased sensitivity of the muscle to acetylcholine. Could it be possible that in myasthenia gravis some long-acting, curare-like substance produces a chemical denervation, with resulting sensitization of muscle to acetylcholine? No answer is at hand on this score. (d) *Presence of curare-like barrier at the myoneural junction.* There is no proof of this at hand. It is tempting, of course, to think of the thymus as perhaps elaborating some curare-like substance with resulting effect on the musculature throughout the body. There is no evidence of such a thymic function, and the nearest clinical evidence consists in the somewhat encouraging results of thymectomy.

The enigma of the thymus

It is popular to look upon the thymus as a vestigial tissue to be grouped with the tonsil and the vermiform appendix. It reacts to certain diseases, however, and with various endocrinologic states in an active way, for instance:

Hyperthyroidism	Thymic hyperplasia
Adrenal cortical deficiency	Thymic hyperplasia
Castration	Thymic hyperplasia

All of these conditions are also characterized by creatinuria and muscular weakness. It is too early to state any relationship but our endeavor should be to find some common denominator.

We are accustomed to think of endocrine glands as being tight little boxes, surrounded by capsules, each in a definite location and acting upon each other by remote control. In some instances, however, there are reasons to believe that they are more enmeshed. Sunder-Plassmann (14) has described an interesting thyroid-thymus complex which tends to knit the two organs together in a functional way. He describes the migration of thymus cells to the thyroid when the latter is stimulated by various biologic means. He considers that the two organs are bound together by a

living syncytium and that they exchange products under certain circumstances. Such an organization could explain some of the riddles of thyroid-thymus function.

SUMMARY

Hyperthyroidism and myasthenia gravis may coexist although the association is rare. In this paper six cases from the literature are reviewed and two new ones reported. In general there appears to be a "see-saw" balance between the two conditions. Symptoms of myasthenia may be aggravated when the hyperthyroid condition is brought under control, although the opposite may occur. The cases have all been in females and in a range of adult age groups. The mechanism is not understood but further studies might throw light upon these diseases and upon the greater problem of muscular fatigue in the human being.

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ANDROGENS AND RENAL FUNCTION. EFFECT OF TESTOSTERONE PROPIONATE IN UREMIA DUE TO CHOLERA

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A RELATION between endocrine and renal function was indicated by the work of Korenchevsky and Dennison (1) in 1934. In a detailed study of all the changes in organ weights resulting from castration in male rats, they found that there was an absolute reduction in kidney weight of 32 per cent (or a reduction of 21 per cent relative to the body weight, which was reduced 15 per cent). They (2) also showed that androgenic materials tended to restore the weight of the kidneys to normal in such rats. Selye (3) first demonstrated, in 1939, that the kidneys of *normal* animals were likewise affected by androgens, and he furnished a detailed description of the histologic changes produced. Korenchevsky's group (4) showed that in normal and senile rats, testosterone propionate was effective, having a "slightly stimulating effect," whereas androsterone and "dehydroandrosterone" in the dosages used were not: the result was a 12 per cent absolute increase in kidney weight (33–36 per cent relative increase) following the administration of 1.5 mg. of testosterone propionate five times weekly in animals weighing 400–500 Gm. It was agreed (3, 4, 5) that there was an increase in the size of the convoluted tubules. In greater detail (3), it was shown that the epithelium of the proximal and distal convoluted tubules, in mice treated with testosterone propionate, was hypertrophied, causing an apparent thickening of the cortex of the kidney; and that the hypertrophy extended to the parietal lamina of the glomerulus, in which there developed a brush border similar to that of tubular epithelium. The dosage with which these results were produced was 0.016 to 0.2 Gm. testosterone propionate per Kg. of body weight, a large amount. Other workers (6, 7) were not able to confirm Selye's histologic findings in all respects. Selye (8) referred to the high parietal epithelium of the glomerulus as a "male type" of kidney structure.

Subsequently other features of the mouse kidney were observed to be influenced by sex. Although the glomerular thickening is normally present in both sexes, it is more frequent in males (89 per cent) than in females

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(13 per cent) (9). The normal weight of the mouse kidney also differs, an average being 15.2 mg. in males and 12 mg. in females (10). Renal excretion is not alike in the sexes, mice in particular having a "normal" proteinuria in the male (11), and man and other species having creatinuria in the *absence* of high levels of androgens (12). The human kidney is 11.5 per cent larger in males than in females (6).

Both estrogens[1] and androgens produce an increase in the weight of the kidney; and although the former is of small magnitude, the effects are additive (7). The absence of increased mitotic figures is evidence that the change in the tubular epithelium is not hyperplastic, but hypertrophic (7); and the absence of change in water content is evidence that the tissue (and not its hydration) is increased in amount, in mice (7). In rats and in dogs, the average diameter of the tubules after administration of testosterone increases by 20 per cent and by 7–17 per cent, respectively (6). By analysis of the tissue for purine nitrogen, it has been deduced that the change is related to an increase in the cytoplasm of the tubule cells, or a hypertrophy rather than a hyperplasia.

Selye (18) refers to the production of tubular hypertrophy as a "renotropic" action of steroid hormones, and reports that progesterone and desoxycorticosterone also exhibit it in lesser degree. Whether the pituitary is also renotropic, aside from its evocation of androgens, is debated. Lattimer (6) has observed that compensatory hypertrophy in the unilaterally nephrectomized rat receiving testosterone was as great, whether the rat was hypophysectomized or not; whereas Selye (18) claims a greater effect if the pituitary is present.

Among androgens which are renotropic, the effort has been made to find one which is minimally androgenic, beginning with the suggestion of Korenchevsky (5) that androsterone was as active as testosterone but might be more suitable because it would not stimulate sexual function in acutely ill males and would not masculinize females. The impression that

[1] Estrogens are reported to be toxic to the kidney, producing degenerative changes if any (5). Kidney weight is said (13) to be decreased temporarily and to return to normal despite continued administration of estrogens. The results of Pfeiffer *et al.* (7) are discounted as due to edema caused by estrogens (8). Remarkable degenerative changes are described following administration of diethylstilbestrol (14). Clinical implications regarding estrogen therapy have been drawn. In one instance, a nephritic woman treated with "Progynon," any possible harmful influence is disputed (15); and in another, the blood urea of a woman with hypertension and renal insufficiency was unchanged by steroid estrogen therapy (16). Innumerable other unreported cases demonstrate that these experimental findings have no significant bearing upon estrogen therapy, but also that estrogens have not a useful application as yet in improving renal function. The outstanding exception is the use of estrogens for the purpose of elevating blood citrate, for the prevention of urolithiasis in bedridden subjects (17).

it is equally active is not, however, well borne out (19). Apparently the most active of all renotropic steroids is either androstane-3(α),-17(α)-diol or its 17-methyl derivative, but these are likewise potent androgens. The difference between these and testosterone esters is less than 10 per cent in renotropic activity, the one being more, the other less effective than testosterone acetate-propionate (for example); whereas the ratio of renotropic to androgenic potency places all these substances in somewhat similar positions, with the experimental combination of testosterone and estradiol suggesting a possible advantage (19). More profound differences would be required to justify recourse to an experimental androgen of limited availability in preference to testosterone.

Other effects of androgens on renal and related functions include: a) lack of effect upon the blood pressure (6, 20, 21), excepting on intraperitoneal administration of hormone (22) and one experiment (23) reported with extremely incomplete data; b) increase in renal acid phosphatase in proportion to weight of the kidney with absolute decrease in alkaline phosphatase (except in the rat, where the reverse obtains), and increase in arginase, provided potent androgens are used, as feeble androgens decrease it relative to the size of the kidney (23); c) acceleration of the compensatory hypertrophy of the remaining kidney following nephrectomy, in rats (6, 25) and in dogs (6); d) certain increases in renal tubular function demonstrable in some species (rat (6), dog (6, 20)) but possibly not in man (26, 27); e) a protective action upon the kidney subjected to harmful agents such as mercuric chloride (28).

Detailed reference to some of the latter findings is desirable.

The use of unilateral nephrectomy as a test for renotropic activity, which is evaluated according to the extent to which the remaining kidney hypertrophies, has an essential logic and great discriminatory value in choosing therapeutic steroids. McKay (25) showed that the renal hypertrophy, when referred to body surface area, amounts to 49 per cent in testosterone-treated rats, as compared with 29 per cent in control rats, whereas castration did not have any significant influence. The most extensive reported work is that of Lattimer (6), who showed that when rats were given 2 mg. of testosterone propionate daily (body weight, 160–200 Gm.) from the time of nephrectomy and for twenty-four days continuously, the remaining kidney reached 98 per cent of the weight of the two kidneys together in intact animals, whereas untreated animals had a kidney of only 76 per cent of that weight. His figures are highly revealing in respect to the duration of treatment, length of time ensuing for recovery, and dosage of androgen; they are cited at length. Using 1 mg. daily for five weeks, the remaining kidney was not significantly different from that of control ani-

mals. Using 5 mg. daily for only ten days, a small difference appeared—72 per cent as compared with 64 per cent. When the androgen administration was deferred for a long time (110 days) and the 2 mg. dosage then given, the treated animals had a kidney with 95 per cent of the weight of the two intact kidneys of control animals, as compared with 82 per cent in the untreated, unilaterally nephrectomized controls. This shows that even the untreated rat continues to develop its remaining kidney towards the weight of the original two kidneys combined—but the accelerating effect of testosterone, which produced in 24 days what was not yet reached in 134 days without treatment, is rather obvious. Comparable results, which the author terms only "suggestive," were found in dogs, in which the ratio *kidney weight/body weight* was 6.38 in 3 treated dogs (10 mg. testosterone propionate daily for four weeks) as against 4.51 in 2 untreated dogs.[2]

It is customary at present to appraise renal function in terms of the quantities of chosen substances transferred to the urine, a field of study which has acquired a large and authoritative literature, provided the tenuous quality of the underlying assumptions is not entirely forgotten. For example, inulin and mannitol are thought to represent purely glomerular filtration; p-aminohippuric acid and diodrast in low concentrations, to serve as a measure of renal blood flow; and the maximum rate at which these latter can be removed, as a measure of optimal tubular function (making, of course, certain assumptions purporting to discount the simultaneous activity of the glomeruli). Welsh *et al.* (20) have tested the actions of testosterone propionate in female dogs according to these assumptions, and found that the maximum diodrast clearance (in this jargon, "diodrast T_m") was more than doubled in two animals and increased 44 per cent in a third animal, using 100 mg. of hormone daily for six to twenty-one days (the weight of the dogs being unknown). The rate of return to normal varied from rapid to very delayed, after treatment was discontinued. These investigators debated whether it was a functional or an anatomic change in the tubules which should be ascribed to the hormone in explanation of this effect; and it was recalled that the anatomic change, for instance in the mouse, may be only 30 per cent, whereas the functional difference is 100 per cent. In any event, the renal tubules must be counted among the tissues profiting by the protein anabolic activity of androgens.

Renal function in man was changed in many inconstant ways by the administration of testosterone propionate. Using 25 mg. daily for two weeks, Lattimer (6) found no significant changes in inulin clearance or diodrast

[2] Ratios were obtained by dividing kidney weight in *grams* by body weight in *kilograms*. The values are actually 0.00638 and 0.00451, respectively.

T_m in 2 normal men or in 3 patients with solitary kidneys; but in a male castrate, inulin clearance rose 23 per cent. In 2 nephritic patients with hypertension, inulin was increased 11 and 5 per cent and diodrast clearance 4 and 5 per cent; it is not clear that small changes such as these are significant. In 2 patients with recent nephrectomy, the one receiving testosterone showed better diodrast clearance (39 per cent vs. 4 per cent) while the one receiving no hormone showed better inulin clearance (21 per cent vs. 11 per cent); treatment had begun on the ninth postoperative day. In another patient, beginning treatment on the twentieth day, both inulin (7 per cent) and diodrast (23 per cent) clearances were increased. In a comparable series, 4 normal subjects and 4 patients with essential hypertension and chronic pyelonephritis showed no significant differences in functional tests of this kind (26). The same lack of demonstrable effect appeared in a series of 9 cases (27) including males, a female, a eunuchoid individual and patients with hypertension and pyelonephritis. In that report, however, the authors make the only significant statement in this field of study, *viz.*: "It is possible, therefore, that although the administration of testosterone . . . did not alter the filtration rate nor renal blood flow or T_m PAH or T_m G, other renal functions might have been affected." This acknowledges the possibility for which we have new evidence of an entirely different kind, and which makes it perhaps unnecessary to rely upon these highly presumptuous indices which under the best of circumstances fail to reveal important functional differences in nitrogen metabolism generally, if not renal function specifically.

The protective action of testosterone on renal structure and function of the rat kidney was demonstrated by Selye (28) by injuring the kidney with mercuric chloride. The animals receiving androgen incurred less tissue damage and were functionally superior to the controls. When the ureter was ligated, likewise, the use of testosterone prevented the atrophy that ordinarily results (29). The amazing observation was made that not only was the atrophy inhibited, but the tubules of treated animals exhibited actual hypertrophic changes similar to those seen normally.

These instances of androgenic actions on the kidney under normal and adverse conditions suggest that testosterone might be employed usefully as a means of salvaging renal structure, or of restoring renal function, or of influencing nitrogen metabolism *in some other way* so that renal insufficiency is a less ominous complication of disease. It was suggested by one of us (E. H.) that an action of one of these possible types might be clinically demonstrable, and that the clinical material of choice might be the severe renal failure of cholera.

CLINICAL MATERIAL AND METHODS

During the 1947 cholera epidemic in Egypt, we undertook an initial evaluation of testosterone propionate in renal insufficiency and uremia. According to Strong (30) "Uremia is the most frequent and fatal complication and in different epidemics it has caused from 15 to 25 per cent of the total deaths." In well-established uremia the prognosis is extremely poor, and the mortality is frequently 100 per cent. At the Tanta Fever Hospital, "Before using the testosterone 70 per cent of uremic cholera patients died in Tanta." General supportive measures were the same for these cases as for those receiving testosterone.

Unfortunately, owing to chaotic circumstances peculiar to epidemic cholera, we were able to keep dependable records in only 27 patients treated with testosterone propionate, whom we observed carefully at first hand. Other patients were treated, but it was impossible under the circumstances to follow them carefully enough to warrant inclusion in this study. Our initial trials were so strikingly successful that we quickly exhausted our limited supplies of hormone and had to obtain more locally with great difficulty.

The first series was treated in Tanta, Egypt, and consisted of 17 patients aged 15 to 40, of both sexes. We planned a basic testosterone propionate course of 25 mg. daily for five days, by intramuscular injection, in addition to the established procedures for cholera (fluids orally and by vein, electrolytes, glucose, alkali) and new chemotherapeutic procedures such as phthalylsulfacetimide, concerning which we will report separately. Patients were chosen for the study if they showed clinical evidence of acute uremia, such as drowsiness, apathy, headache, oliguria or anuria, and albuminuria with red cells and casts; in addition to the usual symptoms of cholera (vomiting, diarrhea, tachycardia, hypotension, "medical shock," dehydration and toxemia).

When testosterone was administered, the production of urine was resumed after a period of usually a few hours. It then increased steadily in amount, the albumin disappeared, the blood urea declined at a sharp rate (or if rising, it ceased to rise and rapidly returned to normal levels), and the clinical course progressed favorably. In this series of 17 cases, three patients died, the first on the third day of testosterone therapy. The second patient passed 1500 cc. of urine loaded with pus on the third day of testosterone therapy and on the fourth day developed severe epistaxis which ended in death. The third patient received only one injection of testosterone, expiring before the second injection could be given.

Encouraged, we undertook to treat an additional 10 patients in Cairo under more favorable conditions. We were able to secure complete clinical

and laboratory data in 7 of these cases, which we present in brief abstract below. There were 2 deaths (cases 6 and 7). We administered 25 or 50 mg. testosterone propionate daily for four to six days, consecutively when possible, depending upon availability. The preparation administered was "Oreton" (Schering). The effects which we believe are traceable to this treatment were: 1) progressive increase in urinary output, beginning a few hours to a few days after the hormone therapy was initiated, 2) rapid decline in the blood urea, and 3) disappearance of albuminuria, which in most instances was of 4-plus grade when treatment began. The significance of these changes is the resumption of kidney function and the control, or inhibition, of further kidney damage. The fact that the mortality rate of our testosterone-treated patients at Tanta was significantly lower than that of patients receiving the same supportive therapy without testosterone indicates, in our judgment, that the restoration of renal function may be attributed to the added testosterone therapy and was a life-saving procedure.

CASE HISTORIES

1. WK 9374, admitted November 2. A 28-year-old woman in the fifth month of pregnancy was admitted with a four-day history of epigastric pain, diarrhea and occasional vomiting. Owing to her drowsy, apathetic condition, details of the history were unobtainable.

Examination revealed a dehydrated, excessively thirsty, desperately-ill woman with sunken eyes, moist tongue, generalized cyanosis, cold, inelastic skin, and carpopedal and laryngeal spasm. There was inspiratory stridor. The pulse was full, rate 96, blood pressure 104/70, blood specific gravity 1060. Severe trachoma was present, with light perception limited to the left eye.

At once the patient was given 500 cc. of 2 per cent sodium bicarbonate solution, 1500 cc. of normal saline, and 20 cc. of calcium gluconate, intravenously, whereupon the spasms disappeared and the blood specific gravity fell to 1051, but the blood pressure was only 90/40. In addition, she received 1900 cc. of water by mouth. The urine excreted on the first day was only about 200 cc. (some having been lost to measurement).

On the second day her general condition was fair, with no further tetany but with cold extremities. There were 7 stools amounting to 600 cc. Fluid intake was 2100 cc. Blood pressure was 90/40. Urine output was undetermined.

She miscarried on the fourth day, and her condition became exceedingly bad, with cold extremities and imperceptible pulse. There was some delay in the delivery of the placenta. She was given 300 cc. of plasma, 1500 cc. of normal saline. The blood pressure was then 90/64 and the pulse 100.

On the fifth day her general condition was improved, with a full pulse and a blood pressure of 96/66. She passed 750 cc. of urine during this day, and had 4 stools totalling 900 cc. On the next day, the sixth, however, her condition had deteriorated; on the seventh day the urine contained albumin and white cells, and a systolic murmur was heard. On the ninth day she was conscious, but drowsy, with a pulse of 112 and blood pressure 90/60. An urticarial rash appeared over the lower extremities. A fetid vaginal discharge was present; but the abdomen was lax and not tender. There were 11,000 leucocytes, with 77% polymorphonuclears, 18% lymphocytes, 4% mononuclears, and

1% eosinophiles. The urine showed a heavy trace of albumin, and was 1000 cc. in amount (with fluid intake totalling 2300 cc.). The blood urea was 320 mg. per 100 cc. on the tenth day.

On the eleventh day, treatment with testosterone propionate was begun, consisting of 25 mg. intramuscularly on alternate days for 5 doses.

On the eleventh day, she received 2300 cc. of fluid by mouth, plus 500 cc. of normal saline and 500 cc. of bicarbonate solution intravenously. She passed a total of 1020 cc. of alkaline urine, with albumin present. Although she was still drowsy, her condition appeared slightly better; and the rash was fading. On the following day her fluid intake and output were the same; the blood pressure was 105/80 and the blood urea was 280 mg. per 100 cc. On the fourteenth day her condition was good. The urine totalled 1500 cc. and still contained albumin. The rash had faded. Two days later, although she remained apathetic, her condition seemed to have improved further. By the seventeenth day the blood urea was 100 mg. per 100 cc., the blood pressure was 110/70, and there were only 2 formed stools. Two days later the urea had fallen to 26 and the urine was normal in character and quantity.

Stool cultures had been positive for *V. comma* on admission, but 5 cultures thereafter had been negative.

In this patient, the decline of the blood urea to the normal level and the disappearance of albuminuria coincided with the administration of testosterone propionate, while the increase in urinary output closely followed treatment.

2. AH 9224, admitted December 3. A man, aged, 45 had had 7 diarrheal stools and vomited four times since the previous morning. On the day of admission he vomited twice and had 4 stools but no abdominal pain. He had been vaccinated for cholera on October 3 and December 3.

Examination disclosed an acutely-ill, dehydrated, cyanotic man with sunken eyes, rapid, weak heart sounds, a pulse of 110, respiration 28, and blood pressure 80/50. The blood specific gravity was 1066, blood urea 78 mg. per 100 cc., and CO_2 combining power 35 vols. per cent. Stools were positive for *V. comma.*

He was treated with 5 Gm. phthalylsulfacetimide immediately and 1 Gm. every two hours thereafter for two days; and in addition he received 3500 cc. of normal saline with 20 Gm. sodium bicarbonate by vein. The urine contained albumin, granular casts, and red, white and epithelial cells; it was 200 cc. in volume. On the second day he lost 1700 cc. of fluid in stools and vomitus. The blood pressure was 80/60. The blood specific gravity was 1060, but fell to 1052 following 2000 cc. of saline and bicarbonate. The blood urea rose to 128 mg. per 100 cc. The urine contained albumin and casts in great quantity, and amounted to only 150 cc.; in view of this, treatment with sulfonamides was discontinued.

By the third day there was some improvement, with blood pressure 125/75, but he lost 2700 cc. of fluid in 12 stools, in addition to vomiting; the urinary output was still only 150 cc. On the following day, although he did not vomit, he was still losing 2100 cc. of fluid by rectum. He was apathetic. The urine volume was 50 cc. The blood urea was 194 mg. per 100 cc.

On the fourth day, treatment with testosterone propionate was begun, consisting of 50 mg. by intramuscular injection daily for 4 days and 25 mg. daily for two additional days. On the fifth day his condition continued to be poor: he was apathetic and drowsy or mildly comatose. The blood specific gravity was 1054, pulse was 54, and blood pressure was 130/70. The urine output was still only 50 cc., with much albumin and many red cells. The blood urea was now 202 mg. per 100 cc. He passed 11 stools. Although he was

still drowsy on the following day, the urinary output had risen to 200 cc. On the seventh day, it was 300 cc., and the blood urea was 194 mg. per 100 cc. Two days later he passed 1050 cc. of urine containing only a trace of albumin, the blood pressure was 140/100, and the stools were normal. By the tenth day there were 1100 cc. of urine with no albumin. The blood urea, however, continued to be high even while his condition was improving, but finally declined to 46 mg. and 21 mg. per 100 cc. by the twentieth day, when he was transferred for convalescent care.

In this patient the increase in urine volume immediately followed the administration of testosterone propionate, although an output of as much as 1 liter was not reached until after six days of treatment. The blood urea remained above 200 mg. for four days afterward and then declined steadily to the normal range. Albuminuria, which was very marked on admission, disappeared by the sixth day of androgen therapy.

3. SK 9476. A man, aged 46, was admitted November 13 with a history of three days of vomiting and diarrhea, with 2 to 5 stools daily. He had received a single dose of cholera vaccine a month previously.

On examination he was found to be in bad condition, with cold, cyanotic extremities, sunken eyes, weak pulse, distant heart sounds, lax abdomen, and marked dehydration; the blood pressure could not be obtained. The blood specific gravity was 1063. The stools contained *V. comma*. On the day of admission he passed 600 cc. of urine containing a great deal of albumin. He was given 1500 cc. of saline by infusion and 2300 cc. of fluids by mouth.

On the second day, the blood specific gravity was reduced to 1054, and a blood pressure of 90/60 could be determined. Although he was improving, the eyes remained sunken, the tongue coated, and the heart sounds distant. He passed 2650 cc. in 7 stools, and vomited 200 cc. of fluid. The blood urea was 211 mg. per 100 cc. He received 2000 cc. of saline containing 20 Gm. of sodium bicarbonate, by vein. Phthalylsulfacetimide was given, 5 Gm. at once and 1 Gm. every two hours for 60 doses.

On the third day, the blood specific gravity was still 1054. The blood urea had risen to 264 mg. The urine volume was 400 cc. He passed 3250 cc. of fluid in 5 bowel movements and received 3750 cc. of fluid by mouth. He remained drowsy. In the succeeding two days the blood urea reached 320 mg. per 100 cc., the vomiting and diarrhea continued, and the urine volume was unimproved. By the sixth day, the blood urea was 380 mg. per 100 cc. His condition was regarded as extremely bad, and fluids were forced by mouth and by vein. He voided 1500 cc. of urine containing much albumin.

On the sixth day he began to receive 25 mg. of testosterone propionate daily. By the following day the urine volume was 2200 cc., with much albumin, but the blood urea was now 390 mg. and his condition was generally the same. On the eighth day, however, it declined to 245 mg. per 100 cc., and he began to feel better. The urine volume remained above 2 liters (although albumin was still present) and from this time forward the blood urea, blood specific gravity, and general condition showed continuous improvement. By the nineteenth day, the blood urea was 50 mg. per 100 cc. The patient was then alert and convalescent.

This patient's course was complicated by corneal ulcers and by the presence of bilharzia ova in the urine.

Whereas, in this case, the urine volume had increased to an ample amount even before testosterone propionate was given, the improved volume was not accompanied by a return of renal function sufficient to eliminate waste products such as urea, and not only was there no accompanying clinical benefit but instead his condition deteriorated criti-

cally. The administration of androgen was followed, within two days, by a rapid and constant decline of the blood urea, accompanied by continuous improvement in general condition and ultimate recovery.

4. MF 9485, admitted November 7. This patient was a man, aged 53, who had had 5 ricewater stools, epigastric pain, and 5 episodes of vomiting on the day before admission. Cholera vaccine had been given in one dose three weeks previously.

He was in poor condition, with anxious look, sunken eyes, cyanosis, cold extremities, general dehydration, and weak and distant heart sounds. The blood specific gravity was 1062, urinary volume 700 cc., albumin ++++, and blood pressure unobtainable. He was given 3330 cc. of normal saline containing 40 Gm. sodium bicarbonate, intravenously. Next day the blood specific gravity had fallen to 1046, but the blood pressure could not be determined until, finally, it was read as 50/40. The pulse was weak and the extremities cold. He passed 900 cc. of urine containing albumin. On the third day the blood urea was 125 mg. per 100 cc. In the next two days he appeared to be improving, with a blood pressure of 75/55 and blood specific gravity 1048; he voided 1900 cc. of urine in 24 hours. The blood urea, however, had reached 232 mg. per 100 cc.

On the seventh day he received 25 mg. of testosterone propionate. The blood urea was 186 mg. per 100 cc. On the eighth day he received a second dose of androgen, and the blood urea was 94 mg. The hormone was then deferred for two days and resumed for four days. By the thirteenth day the blood urea was 36 mg., he had a normal temperature, his condition was good, stool cultures were negative, and he was considered convalescent on the sixteenth day.

In this patient, also, the urinary volume had increased even before testosterone was given, but the general condition was not improved and the blood urea was rising rather than falling even with an ample urine output. The blood urea had begun to improve at the time the first dose of testosterone propionate was given, but its most precipitous fall occurred the day after androgen was begun, and manifest clinical improvement followed this event.

5. AA 9523, admitted November 10. A 24-year-old woman complained of one day of mild diarrhea and repeated vomiting followed, on the day of admission, by 7 rice-water stools and 12 episodes of vomiting. She had been vaccinated the day before onset.

Examination showed an acutely ill, cyanotic, dehydrated woman in poor condition, with cold extremities, weak pulse and distant heart sounds. The blood specific gravity was 1072 and the blood pressure was unobtainable. She was given 6 liters of saline and sodium bicarbonate, and had a urinary output of 500 cc. Later that day a blood pressure of 95/55 was obtained, the pulse fell to 96 and the specific gravity to 1052. There was some improvement on the second day, but the blood urea was found to be 150 mg. per 100 cc. and she lost 2500 cc. of fluid in the stools. The urine output, however, was now 2100 cc.

On the third day there were 11 stools with a loss of 2650 cc. Extrasystoles were detected. The urinary output fell to 950 cc. Drowsiness was present. Except that the drowsiness was more marked, and the blood urea reached 265 mg., there was no change until the eighth day.

Testosterone propionate, 25 mg., was then given daily for five days. On the ninth day, or the second day of hormone therapy, she had a blood urea of only 122 mg. per 100 cc. There were only 2 stools, the urine volume was 2900 cc., and the blood pressure was 105/60. By the next day she was fully conscious and the blood urea had fallen to 46 mg.

By the last day of androgen therapy, the stools were normal and cultures for cholera vibrio were negative.

The total dose of testosterone propionate had been 125 mg. Its most striking sequel was the fall in blood urea; the urine volume, which had varied greatly, rapidly returned to normal. Marked general improvement occurred during the period of treatment.

6. LO 9422, admitted November 4. This woman, aged 30, was admitted in fair condition after three days of only moderately severe illness, consisting of watery diarrhea and vomiting, both in limited amount.

On admission she was not dehydrated, to judge from physical signs, and general examination showed no remarkable features: the pulse was full, and the skin was warm. There was, however, a urinary volume of only 100 cc. containing albumin, the blood specific gravity was 1068, and respirations were 30 per minute. She was given 3 liters of saline. On the second day her blood urea was 208 mg. per 100 cc., BP 90/70, the tongue was dry and albuminuria was present (1300 cc.). Diarrhea continued and she became drowsy. By the fourth day the blood urea had reached 276 mg. and the urine volume was less than 1 liter; and now râles were heard at both lung bases.

On the sixth day, testosterone propionate, 25 mg. daily, was started and continued for 6 doses. Two days later, with other clinical features unchanged (except for a widely fluctuating urinary output, 600 to 1600 cc.), she developed a morbilliform rash, fading on pressure over the face, arms and to some extent on the trunk. Stools now contained the cholera vibrio. The next, or ninth day, penicillin, 200,000 units daily, was started, and continued for one week. Two large furuncles developed on the trunk. The blood urea reached 330 mg. per 100 cc. There was a polymorphonuclear leucocytosis (11,000 W.B.C., 77% PMN) on the following day. She was regaining consciousness, but by the thirteenth day she passed into an agitated state. There was normal temperature, the blood urea was 95 mg., and stools were negative for cholera. On the fifteenth day her rash was becoming generalized and there was a blood urea of 88 mg. (on the next day, 77 mg.). Basal râles were still present, but penicillin was discontinued, as the temperature was normal.

The terminal course seemed to begin on the nineteenth day. The temperature again rose, the patient appeared to be psychotic, and albuminuria was present. Penicillin, 100,000 units daily was started. After one week the blood pressure was read as 50/? and the chest signs were more marked, with consolidation in the right upper lobe. The blood urea rose to 142 mg. The patient became comatose and died.

Autopsy revealed lobar pneumonia, with post-cholera changes in the liver and intestines; but the kidneys were normal. An excerpt from the pathologic findings reads as follows:

"Kidneys: The glomeruli are normal, the tubules are normal; there is no interstitial inflammation. Arteries show very slight sclerosis, but the arterioles are normal."

In this patient, the proximate cause of death was pneumonia. There had been urinary findings typical of uremia in cholera, which, following the administration of testosterone propionate, had shown continuous improvement. Had additional infection not supervened, recovery had been possible in this patient, and indeed seemed to have been well established in the first sixteen days of her course.

7. AA 9617. A 35-year-old man was admitted November 16 with a one-day history of diarrhea and vomiting.

On admission his condition was poor, with dehydration, cyanosis, cold skin, weak

pulse, and distant heart sounds. He was anuric, and the blood specific gravity was 1065. The blood urea on admission was 147 mg. per 100 cc.

On the second day, in addition to fluids, testosterone propionate 25 mg. was given, and was repeated daily for 4 doses. The patient was drowsy, with respirations of 110 per minute and blood specific gravity 1060. Vomiting and diarrhea continued. By the third day his condition was even worse: temperature 102° F, pulse 82, respiration 26, blood pressure 110/70, with 5 green fluid stools totalling 1600 cc. The blood specific gravity was 1056. He passed 900 cc. of albuminous urine. The stools contained the cholera vibrio. On the fourth day the blood urea was 286 mg., pulse 62, and blood pressure 90/60; he was losing 2500 cc. of fluid in stools and vomitus. For several days thereafter the stool cultures were negative and temperature was normal; but his general condition remained unsatisfactory, and finally deteriorated rapidly. He died in pulmonary edema on the tenth day.

The disease process in this patient was not fully understood clinically, for even during the administration of testosterone the blood urea rose and the urine volume became smaller. While, for practical purposes, the cholera was controlled with phthalylsulfacetimide, the patient failed to survive an unidentified complication. *Autopsy* is quoted in part as follows:

> "Heart: several foci of calcified necrotic tissue surrounded by a chronic inflammatory reaction. Lungs show slight interstitial pneumonia. Kidneys: tubules are markedly dilated, lumina containing precipitated protein; there is slight interstitial edema. Slight inflammation of the renal pelvis. Blood vessels are normal."

Cholera exemplifies the group of disorders manifesting "medical shock" with circulatory collapse and secondary renal failure, the latter being attributed variously to loss of filtration pressure, anoxia and specific toxemia. The customary program of fluid administration in cholera is relatively effective, whichever of these mechanisms may be chiefly concerned, and yet about one-quarter of the deaths in cholera result from renal failure. The overall mortality rate in the past epidemic is announced officially to be 49.2 per cent. We administered testosterone propionate exclusively to patients manifesting clinical evidences of uremia, and were able to follow 27 satisfactorily. The mortality in these 27 cases was 5, or 18.5 per cent. One of these patients was lost before the androgen treatment could be well instituted, only one injection having been given. One patient died on the third day of testosterone therapy and one on the fourth day. Autopsy reports on these two patients are not available. They may or may not have received adequate testosterone therapy. One died following what we thought was adequate androgen therapy and autopsy findings in this case, number 6, showed that the kidney had recovered from all injury. Testosterone therapy was a definite failure in case 7 as the autopsy showed "tubules are markedly dilated, lumina containing precipitated protein; there is slight interstitial edema;" and the heart contained multiple necrotic and inflammatory foci.

On the basis of experimental studies which we have cited, we believe

that testosterone propionate has a direct action on the kidney. There is an alternative explanation for its effects, namely, that under the influence of testosterone propionate nitrogen metabolism is modified in such a way that the end-products cease to accumulate, and possibly participate in useful tissue chemistry instead. Opposed to such an explanation are the facts that the urinary nitrogenous substances are not themselves toxic, the functional capacity of the kidney in these cases actually improves as shown by the relief of oliguria, and the albuminuria clears up *pari passu* with the other gains. Localizing the action to the kidney, and even to the tubular mechanism, we are unable, however, to specify what this action may be. The fact that testosterone propionate can promote tubular hypertrophy in the face of hydronephrosis (28) implies a powerful sustaining and developmental influence on this form of tissue, and numerous experiments cited suggest that this influence is accompanied by enhancement of function. The significance of albuminuria and its abatement is beyond speculation in view of the limitations of space.

SUMMARY

The literature indicating an important physiologic action of testosterone on renal structure and function is reviewed as it applies to the control of clinical uremia. We report our treatment in 40 cases of cholera with uremia by means of 25–50 mg. of testosterone propionate daily, in addition to the established methods of treating cholera. The mortality in 27 cases which could be satisfactorily followed under epidemic conditions was 5, or 18.5 per cent. One of these patients died before the hormone treatment was more than begun. Before the institution of added testosterone propionate therapy, the mortality rate of cholera patients with uremia at Tanta Fever Hospital was 70 per cent. We realize full well that in such a limited number of cases mortality statistics are not strictly applicable; nevertheless, it is our firm belief that testosterone propionate is beneficial in this form of uremia. The possible mechanism by which this benefit is exerted is discussed. It is hoped that this report will encourage further investigation concerning the clinical usefulness of testosterone propionate in disease states complicated by impaired renal function.

ACKNOWLEDGMENT

Routine autopsies were performed in cases 6 and 7 by the hospital authorities in Cairo. Subsequently, gross specimens of the spleen, gonads, brain, heart, lungs, liver, stomach, small intestines, and kidneys from these two patients were brought to the United States for further histopathologic study. We are very grateful to Dr. J. E. Flynn, Assistant Professor of Pathology, Columbia University College of Physicians and Surgeons, for

detailed pathologic reports on these two cases. It is significant that Dr. Flynn's findings in every way confirm the report of the hospital pathologist in Cairo.

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PROPYLTHIOURACIL IN THE TREATMENT OF TOXIC GOITER

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THIS report, an extension of one previously made (1), deals with the use of propylthiouracil in 95 patients with toxic goiter during a period of twenty-one months. The group includes 67 patients with toxic nodular goiter (21 males and 46 females), and 28 with toxic diffuse goiter (8 males and 20 females). The average age of the former was 51 years with a duration of the disturbance of 2.7 years; in the latter it was 37 years and the duration 3.7 years. Thirty-four patients, 24 with toxic nodular and 10 with toxic diffuse goiter, had been previously treated with thiouracil, and 9 had had iodine before treatment.

The average initial basal metabolic rate of the untreated patients was plus 24 per cent for those with toxic nodular goiter; and plus 30 per cent for those with toxic diffuse goiter. Both types previously treated with thiouracil showed an average initial basal metabolic rate of plus 6 per cent (Table 1).

TABLE 1

Type of goiter	No. of patients	Average age. Yrs.	Duration of disease. Yrs.	No. of patients receiving iodine previously	No. of patients receiving thiouracil previously	Average initial basal metabolic rate (%)	
						In patients treated with thiouracil previously	In untreated patients
Toxic nodular	57 (21 ♂) (46 ♀)	51	2.7	7	24	+6	+24
Toxic diffuse	28* (8 ♂) (20 ♀)	37	3.7	2	10	+6	+30

* In 11 patients the disease was recurrent.

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DOSAGE AND TIME OF ONSET OF REMISSION

Previously untreated patients with toxic nodular goiter required initially an average of 140 mg. of propylthiouracil daily, usually divided into three equal doses. Those with toxic diffuse goiter required 166 mg. daily. The dosage in each group ranged from 25 to 300 mg. daily, the smaller dose being used at first and found inadequate. The average initial dose was 150 to 200 mg. daily and this was reduced or increased according to the response of the patient. The patients transferred from thiouracil therapy needed between 35 and 43 mg. daily for maintenance of remission.

In the patients with toxic nodular goiter remission appeared in an average of eight weeks and was maintained with from 50 to 150 mg. of the drug daily. In the patients with toxic diffuse goiter remission appeared in ten weeks and required a similar amount of the drug daily for maintenance. Previously administered iodine did not delay the response appreciably.

TOXIC REACTIONS AND BLOOD CHANGES

Only one patient, a woman with recurrent toxic diffuse goiter, developed drug fever forty-one days after beginning treatment. This was the only toxic reaction of importance in the entire group. Five patients in whom toxic reactions occurred from thiouracil were able to take propylthiouracil without similar difficulty.

Leucocyte counts as low as 3000 per cu. mm. were encountered in several patients but these were not accompanied by reduction in the polymorphs and no ill effects followed the uninterrupted administration of the drug. One patient, a 58-year-old woman with a toxic nodular goiter, showed an initial leucocyte count of 3500 with 61 per cent polymorphs, followed by a reduction to 3000 cells and 54 per cent polymorphs after administration of 300 mg. of propylthiouracil daily for two weeks. After two more weeks the leucocyte count was 3050 with 39 per cent polymorphs and therefore the drug was stopped although there were no disturbing symptoms. Two subsequent weekly counts showed 5000 cells with 37 per cent polymorphs and 4200 cells with 71 per cent polymorphs. Treatment was resumed with 200 mg. daily and after three weeks the leucocyte count was 3200 with 65 per cent polymorphs. Two weeks later it was 3600 with 59 per cent polymorphs, and since the patient was in remission, the drug was discontinued.

This was the only instance in which the drug appeared to have a depressing effect on the white blood cell count.

When all the lowest leucocyte counts in the series were averaged, the figures were 5050 for those with toxic nodular and 5700 for the toxic diffuse goiter patients. The average of the lowest percentages of polymorphs in each patient was 65 for each group (Table 2).

TABLE 2

Type of goiter	Average initial daily dose (mg.)		Daily maintenance dose (mg.)	Length of time until onset of remission (wks.)	Average of lowest leucocyte counts (cells per cu. mm.)	Average of lowest percentages of polymorphs
	In patients treated with thiouracil previously	In untreated patients				
Toxic nodular	43	140	85	8	5050	65%
Toxic diffuse	35	166	90	10	5700	65%

DURATION OF TREATMENT AND PERSISTENCE OF REMISSION

A number of patients were given the drug for an extended period beyond the remission stage in order to determine the effect of prolonged administration. This procedure necessarily raised the average duration of treatment to 8.6 months for those with toxic nodular goiter and ten months for those with toxic diffuse goiter. No evidence of intolerance or toxic reaction was observed in any of the patients treated for as long as sixteen months. One patient, otherwise successfully controlled, complained of a persistent bitter taste after two months' treatment. This continued for three months then gradually disappeared.

Remissions have persisted in 24 patients with toxic nodular goiter, 3 males and 21 females, for varying periods of time after an average treatment period of 11.8 months. Two additional patients had a relapse and had to resume treatment, one after five months of remission and one after two weeks (Table 3). From Table 3 we also observe the following:

In the 24 patients in whom remissions have persisted the toxicity was mild in 19 and severe in 5. The average initial BMR was plus 24 per cent. Only 1 patient was treated for less than 6 months. One patient was symptom-free for 2 months; 1 for 4 months; 3 for 6 months; 2 for 7 months; 3 for 8 months; 2 for 10 months; 2 for 11 months; 2 for 12 months; 1 for 13 months; 1 for 14 months; 2 for 15 months; 2 for 17 months; 1 for 18 months; and 1 for 19 months.

Assuming that remissions of six months or longer are sustained, 22 patients with toxic nodular goiter may be considered in sustained remission.

Nine patients with toxic diffuse goiter (2 males and 7 females) have been in remission for two to eight months after an average treatment period of fifteen months. Four of these had recurrent toxic goiter. Table 4 shows:

TABLE 3

REMISSIONS (2 RELAPSES) IN 26 PATIENTS WITH TOXIC NODULAR GOITER TREATED WITH PROPYLTHIOURACIL

Patient	Age and sex	Duration of disease	Severity*	Thyroid	Initial B.M.R. %	Final B.M.R. %	Duration and amount of treatment†		Length of remission and results‡
							with thiouracil	with propylthiouracil	
	(yrs.)								
1. M.A.	42 F	2 wks.	S	Bilateral nodular	+51	−6	10 mo. (600–100)	10 mo. (25–75)	13 mo. Gained 3.1 Kg.; thyroid unchanged.
2. R.A.	39 F	10 mo.	M	Bilateral nodular	+20	−6	4 mo. (300–200)	5 mo. (100)	11 mo. No weight change; thyroid smaller.
3. M.A.	66 F	?	M	Left nodular	+13	−2		9 mo. (150–50)	6 mo. Gained 3.1 Kg.; thyroid unchanged.
4. B.B.	62 F	8 mo.	M	Bilateral nodular (substernal)	+33	−21		10 mo. (75–25)	11 mo. No weight change; thyroid unchanged; persistent lid lag.
5. L.B.	64 M	3 yrs.	M	Bilateral nodular (substernal)	+15	−20	31 mo. (600–100)	8 mo. (50)	12 mo. No weight change; thyroid smaller.
6. B.C.	62 F	1 yr.	M	Bilateral nodular	+30	− 5	9 mo. (800–600)	4 mo. (25–75)	17 mo. Gained 2.3 Kg.; thyroid much smaller.
7. M.F.	48 F	1 yr.	S	Bilateral nodular	+43	−10	reaction 1 mo. (400–300)	15 mo. (50)	8 mo. Gained 4.5 Kg.; thyroid much smaller.
8. M.G.	46 F	2 mo.	M	Right nodular	+20	− 1	9 mo. (600–200)	7 mo. (50–75)	15 mo. Gained 1.8 Kg.; thyroid unchanged.
9. M.H.	58 F	?	M	Bilateral nodular	+16	−25		6 mo. (300–200)	4 mo. No weight change; thyroid smaller.
10. E.H.	62 F	1 yr.	M	Bilateral nodular	+19	−5		8 mo. (150–25)	6 mo. Gained 2.3 Kg.; thyroid unchanged.
11. E.L.	56 F	2 mo.	S	Bilateral nodular	+27	−13	3 mo. (600–200)	5 mo. (75)	17 mo. Gained 11 Kg.; thyroid much smaller.
12. I.L.	29 F	6 yrs.	M	Nodule in isthmus	+12	− 9		6 mo. (150–50)	14 mo. Gained 0.9 Kg.; thyroid unchanged.
13. M.M.	27 F	1 yr.	M	Bilateral nodular	+10	− 1	9 mo. (600–200)	15 mo. (50–100)	10 mo. Gained 6 Kg.; thyroid smaller.
14. E.M.	36 F	3 mo.	M	Not palpable	+24	−13		4 mo. (150–50)	7 mo. Gained 6 Kg.; thyroid unchanged.
15. M.M.	65 F	?	M	Right nodular (substernal)	+14	− 4		15 mo. (100–150–50)	6 mo. No weight change; thyroid unchanged; improved control of diabetes.
16. D.M.	50 F	6 wks.	S	Right nodular	+44	−10		9 mo. (150–50)	2 mo. Gained 2.3 Kg.; thyroid smaller; lid lag persistent
17. L.N.	64 M	1 yr.	M	Nodule in isthmus	+18	−14		11 mo. (150–100)	8 mo. Gained 3.1 Kg.; thyroid unchanged.
18. M.N.	70 F	20 yrs.	M	Left nodular	+80	− 5		6 mo. (200–100)	12 mo. Gained 10 Kg.; thyroid unchanged.
19. J.P.	35 F	4 yrs.	M	Not palpable	+13	−15	6 mo. (200–300–200)	4 mo. 50	18 mo. Gained 3.1 Kg.; thyroid unchanged.
20. E.R.	76 F	4 yrs.	S	Bilateral nodular	+33	−7	30 mo. (800–100)	15 mo. (25–50 100)	5 mo. followed by *Relapse.* Gained 4.5 Kg.; thyroid unchanged.
21. E.R.	49 F	2 mo.	M	Right nodular	+16	− 9	1 mo. (400–200)	5 mo. (25)	19 mo. Gained 0.9 Kg.; thyroid smaller.
22. L.S.	40 F	16 mo.	M	Nodule in isthmus	+11	− 1		13 mo. (75–50)	7 mo. Gained 2.3 Kg.; thyroid smaller; lid lag persistent.
23. H.S.	38 F	2 wks.	S	Nodule in isthmus	+44	− 9	5 mo. (400–100)	7 mo. (25)	15 mo. Gained 5 Kg.; thyroid smaller.
24. M.S.	51 F	6 mo.	M	Nodule in isthmus	+18	−11		9 mo. (100–50)	10 mo. Gained 3.6 Kg.; thyroid smaller.
25. B.T.	50 F	7 yrs.	S	Bilateral nodular	+22	+ 1	15 mo. (800–300)	14 mo. (50–150)	2 wks. Followed by *Relapse.* No weight change; thyroid unchanged.
26. M.T.	70 M	?	M	Right nodular	+12	−22		6 mo. (200–50)	8 mo. Gained .9 Kg.; thyroid unchanged; improved control of diabetes.

* "S": Severe; "M": Mild.

† Figures in parentheses indicate daily dosage range of drug in milligrams.

‡ Patients in remission were free of nervousness, tremor, tachycardia and sweating. Eye signs showed improvement unless otherwise indicated.

TABLE 4. REMISSIONS (4 RECURRENCES) IN 9 PATIENTS WITH TOXIC DIFFUSE GOITER TREATED WITH PROPYLTHIOURACIL

Patient	Age (yrs.) and sex	Duration of disease	Severity*	Thyroid	Initial B.M.R. %	Final B.M.R. %	Duration and amount of treatment†		Length of remission‡ and results
							with thiouracil	with propyl-thiouracil	
1. V.H.	30 F	1 yr.	M	Bilateral enlargement	+25	−12		10 mo. (150–50)	7 mo. Gained 1.3 Kg.; thyroid smaller.
2. P.H.	16 F	1½ yrs. recurrent	M	Bilateral enlargement	+22	−15	3 mo. (600–200)	14 mo. (50)	2 mo. Gained 2.7 Kg.; thyroid smaller.
3. D.J.	27 F	2 mo.	M	Bilateral enlargement	+10	−13		13 mo. (50–25)	8 mo. Gained 2.3 Kg.; thyroid smaller.
4. R.F.	62 M	3 mo. recurrent	M	Not palpable	+10	−10	3 mo. (100)	5 mo. (25)	8 mo. Gained .9 Kg.; thyroid unchanged.
5. E.K.	52 F	12 yrs. iodine 12 yrs.	S	Bilateral enlargement (hard)	+15	−24	15 mo. (600–100)	16 mo. (25–50)	5 mo. Gained 7.2 Kg.; thyroid smaller; exophthalmos unchanged.
6. B.L.	31 F	6 yrs. recurrent	S	Not palpable	+23	−16	6 mo. (300–200)	18 mo. (25–50)	4 mo. Gained 2.7 Kg.; thyroid unchanged; exophthalmos unchanged.
7. F.M.	39 F	9 mo. recurrent	S	Bilateral enlargement	+10	−20	10 mo. (400–100)	14 mo. (25–50)	7 mo. Gained 7.2 Kg.; thyroid smaller; exophthalmos dimin'd.
8. L.S.	30 F	1 yr.	S	Bilateral enlargement	+23	+ 2		5 mo. (150)	7 mo. Gained 10 Kg.; thyroid smaller.
9. H.U.	28 M	3 mo.	S	Bilateral enlargement	+ 7	− 7		3 mo. (300–100)	4 mo. Gained 10.4 Kg.; thyroid smaller; lid lag persistent.

* "S": Severe; "M": Mild.

† Figures in parentheses indicate daily dosage range of drug in milligrams.

‡ Patients in remission were free of nervousness, tremor, tachycardia and sweating. Eye signs showed improvement unless otherwise indicated.

The toxicity was mild in 4 and severe in 5 patients.

The average initial BMR was plus 16 per cent.

Two patients were treated for less than 6 months.

One patient was symptom-free for 2 months; 2 for 4 months; 1 for 5 months; 3 for 7 months; and 2 for 8 months.

Five of this group may be considered in sustained remission.

Out of this entire series, 27 patients (28 per cent) are now in sustained remission.

DIABETES AND TOXIC GOITER

Of the 10 patients with this combined disturbance, 2 had developed diabetes after recurrence of surgically treated toxic diffuse goiter. One was a man aged 47 in whom diabetes appeared two years after thyroidectomy and the other a 54-year-old woman in whom it appeared twenty years after surgery. In neither patient was diabetic control made easier either through

the use of thiouracil or later with propylthiouracil, although the toxicity was adequately controlled.

Both conditions improved in 6 patients in whom the diabetes antedated the thyrotoxicosis (all of these had toxic nodular goiter), in a manner typified by the response of one of this group:

A 57-year-old woman with diabetes of one year's duration required increasing amounts of insulin, up to 100 units PZI daily, with unsatisfactory control. She was found to have a toxic nodular goiter with a basal metabolic rate of plus 16 per cent. Six weeks of thiouracil produced a remission with a BMR of minus 3 per cent and satisfactory control of the diabetes with 10 units PZI daily. Control was maintained following transfer to propylthiouracil and after four months the insulin was discontinued.

In the remaining 2 patients, also with toxic nodular goiter, one, a man aged 67 with diabetes for twenty-two years and thyrotoxicosis for twenty years, and the other a woman of 27 with diabetes for six years and thyrotoxicosis for three years, the response was not as decisive as in the other patients. Both showed remission of the toxic state and control of the diabetes within three months following thiouracil. The man required no insulin (having originally taken 40 units PZI daily) and required none for the next ten months. Since being transferred to propylthiouracil he has required 10 units PZI daily. The woman did not show a reduced need for insulin during thiouracil therapy and has in fact required an increased amount since transfer to propylthiouracil.

While the number of patients observed is too small to permit drawing final conclusions, it appears that where the diabetes has antedated the thyrotoxicosis, propylthiouracil as well as thiouracil may effect improved control of the diabetes through improvement in the thyrotoxicosis.

PREGNANCY AND THYROTOXICOSIS

Three patients have been carried to term with the thyrotoxicosis fully controlled by propylthiouracil. All were delivered of normal infants who developed without evidence of thyroid or other disturbance.

The first of these was a 32-year-old primipara with a toxic diffuse goiter that had been inadequately controlled with iodine during the first five months of her pregnancy. Propylthiouracil was substituted and she was maintained in remission until term on 100 mg. daily. Fifteen minims of Lugol's solution was given daily during the three weeks preceding delivery. Symptoms recurred three months later and remission was induced after six weeks of propylthiouracil. The drug was discontinued after four more months of maintenance treatment and the patient has remained symptom-free.

The second patient was a 30-year-old primipara with an untreated mild toxic diffuse goiter in whom the administration of 150 mg. of propylthiouracil daily was started during the second month of her pregnancy. Response was prompt and satisfactory and control was maintained with the same dose until delivery. Fifteen minims of Lugol's solution was given daily during the last three weeks of the pregnancy. Remission has continued for three months following delivery.

A third patient, a 38-year-old multipara, had had a thyroidectomy in 1932 and a second one in 1941. In April 1945, her physician started treatment with thiouracil because of recurrent thyrotoxicosis and auricular fibrillation. Control was achieved and a maintenance dose of thiouracil was continued. She became pregnant in September 1946 and two months later, when the basal metabolic rate was minus 9 per cent, propylthiouracil was substituted for the thiouracil. During the eighth month she was hospitalized for five days because of false labor pains. Three weeks later she was re-admitted in labor and delivered of a normal baby by cesarean section because of cervical dystocia. The baby has developed normally and the mother has remained in remission for two months following delivery.

COMMENT

Evidence for the efficacy and safety of propylthiouracil as an antithyroid agent is accumulating rapidly. The reports of Appleby (2), Astwood and VanderLaan (3a, b), Beierwaltes and Sturgis (4), Crile (5), Foss and Klinger (6), Jackson (7a, b), Kjerulf-Jensen and Meulengracht (8), Lahey and Bartels (9), Bartels (10), McCullagh (11)(12), McGavack (13), Reveno (1) and Ucko (14), favor this new agent over all other preparations. Only one report, that of Wilson and Goodwin (15), dealing with the comparative effectiveness of propyl- and methylthiouracil, claims that the former has no outstanding advantages over the latter.

In the experience thus far reported in the literature, there is quite general agreement that this new agent has all of the desirable qualities of thiouracil without its disturbing toxicity. Remission usually follows a daily dose of 150 to 250 mg. in eight to ten weeks, appearing somewhat more slowly than with thiouracil and not seriously delayed by previously administered iodine. Exophthalmos and thyroid enlargement recede gradually. There is a notable absence of pronounced weight increase and little myxedema has been encountered. Some depression of the leucocyte count has been noted, but so far only one instance of agranulocytosis (9) has been observed. Frequent blood counts are, however, still considered essential. There are, as yet, few data regarding sustained remissions.

The experience in the present group of 95 patients coincides in the main with that of most observers. The dosage and period of time necessary for remission were practically the same; toxic reactions were few (1.1 per cent)

and not of serious nature; and sustained remissions were observed in 28 per cent.

While the number of patients with combined diabetes and toxic goiter was small and the results accordingly inconclusive, there appeared to be good control of both conditions in those in whom the diabetes antedated the thyrotoxicosis.

Toxic goiter complicating pregnancy was well controlled, with uncomplicated prenatal and postpartum behavior and delivery of normal infants.

SUMMARY

The thyrotoxic state in 95 patients (67 with toxic nodular and 28 with toxic diffuse goiters) was successfully controlled with propylthiouracil.

One patient showed a toxic reaction in the form of drug fever, and one showed a transient white cell count depression with reduction in the percentage of polymorphonuclears.

The average initial dose in those with toxic nodular goiter was 140 mg. of the drug daily and 166 mg. in those with toxic diffuse goiter. It took eight weeks for remission to appear in the former and ten weeks in the latter. An average of 85 to 90 mg. daily was required in both types for maintenance.

There was no evidence of intolerance during prolonged treatment. The average duration of treatment in toxic nodular goiter was 8.6 months and in toxic diffuse goiter, 10 months.

Twenty-two patients with toxic nodular and 5 with toxic diffuse goiter have been in remission without treatment over six months, making a total of 28 per cent in sustained remission.

Of 10 patients with diabetes and toxic goiter, 2 in whom the diabetes appeared after the onset of the thyrotoxic state showed no improvement in control of the diabetes during propylthiouracil therapy. Six of the remaining 8, with diabetes antedating the thyrotoxicosis, showed good control of the diabetes, while 2 did not show as decisive a result.

Three patients with toxic diffuse goiter treated with propylthiouracil were carried through pregnancy successfully, were delivered of normal babies and have continued in sustained remission.

The efficacy and safety of propylthiouracil for inducing remission in all forms of toxic goiter appear well established. Its short-term value in the preoperative preparation of patients has been amply demonstrated, but further observation is still needed to grade its usefulness in prolonged medical treatment.

ACKNOWLEDGMENT

The propylthiouracil was supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc., Pearl River, New York.

The author is indebted to Drs. Roger Siddall, Harold C. Mack, and Nicola Gigante for permission to include the patients with pregnancy and thyrotoxicosis.

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SUPPRESSION OF LACTATION WITH ETHINYL ESTRADIOL

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THE estrogens have proved their usefulness in the control of painful breast engorgement in the immediate postpartum period and in the early suppression of lactation. However, the ideal product, dosage and time of administration have not been reached. An attempt has been made in this study to evaluate the usefulness of ethinyl estradiol for the suppression of lactation after other measures had been discarded for either increased secondary uterine bleeding or for ineffectiveness.

In 1933, Smith and Smith (1) demonstrated the inhibition of lactation in laboratory animals with the use of large doses of estrin. From this point, extensive trials (2–8) were undertaken with oral and parenteral administration to determine the worth of both the natural and the synthetic substances of estrogen potency. The earliest study with ethinyl estradiol was reported by Kurzrok, Livingston and Birnberg (9) in 1942. Their observations on a series of 59 puerperal women showed promising results.

The present study was undertaken after our experience with other measures proved unsatisfactory. As early as 1943, our experience showed that stilbestrol in daily dosage of 1.5 mg. caused an immediate increase in the amount of bloody lochia and an occasional alarming amount of uterine bleeding following withdrawal. From then until early 1947, we reverted to a previous type of medication which included administration of 200 mg. of camphor monobromate capsules four times daily, limitation of fluids, saline purgation and tight breast binding.

The material consists of 501 consecutive private patients of the senior author who were delivered at the Newark Beth Israel Hospital from January 1, 1946 to January 1, 1947 (Table 1). Of that number, 101 or 20 per cent did not attempt to nurse their offspring, mainly because of voluntary refusal and occasionally for one of the following reasons: stillbirth, neonatal death, prematurity, disease of the mother, mastopathy and presence of carcinoma (one case). In 34 instances, 7 per cent, breast feeding was discontinued during the hospital stay because of insufficient milk formation or of incompatibility. One hundred and twenty-eight non-nursing mothers —25 per cent—formed a control series. In them the subsequent pain and engorgement of the mammary glands were treated by the camphor mono-

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* *From the private cases on Obstetrical Service "B".*

TABLE 1. DATA ON 501 POSTPARTUM PATIENTS, SHOWING EFFECT OF ETHINYL ESTRADIOL

	Offspring transferred from breast to bottle feeding	Offspring bottle fed completely	Non-nursing camphor control group	Non-nursing ethinyl estradiol group
Number of patients	34	101	128	238
Per cent of total	7	20	25	48
	All figures below are in per cent:			
During hospitalization:				
Aware of medication given			48	33
Painful breasts		40	57	34
Engorgements of breasts		14	54	26
			Medication discontinued	
After leaving hospital:				
Breast milk overflowed		46	49	60
Breasts became hard		50	25	46
Painful breasts		44	26	43
After leaving hospital it was necessary to:				
Wear a breast binder		37	21	45
Limit fluid intake		34	19	48
Take additional medication for painful breasts		36	14	34

bromate regimen previously outlined. The remaining 238 patients, 48 per cent, did not nurse and lactation was suppressed by the use of ethinyl estradiol according to the following regimen.

Ethinyl estradiol was administered by the nursing staff with other routine hospital medications, in daily dosage of 1.5 mg. in three equally divided amounts. No other supportive measures were undertaken to augment the suppression of lactation. This regimen was started on the day following delivery, or as soon thereafter as possible, and was continued for the duration of the hospital stay, which varied from six to nine days. For the control of further difficulties with pain or engorgement in the breasts after the patient's arrival at home, it was necessary to use breast binding, limitation of fluids and camphor monobromate (in 200 mg. capsules in four daily

doses for a period of four days) since the hospital supply of ethinyl estradiol was limited, nor could it be purchased in such dosage as we were using.

DISCUSSION

Among the 101 mothers who completely breast-fed their offspring during the hospital portion of the puerperium, some 40 per cent experienced pain, whereas only 14 per cent complained of undue fullness in the breasts. In the follow-up period, which lasted from two to nine months, these same women presented further symptoms—40 per cent showed an unduly free overflow of milk constituting leakage, 50 per cent complained of hardness and 44 per cent complained of pain in the mammary glands. Of this number, it was necessary for slightly over one-third to wear a binder, limit fluids and to take camphor medication for the control of pain.

The number of mothers—34—who switched from breast feeding to bottle feeding was statistically too small to present any conclusions. Estrogen substance is of no avail during the period following cessation of suckling as its success depends upon suppression. It will be shown subsequently that camphor and its supportive regimen fails to control adequately the pain of engorgement which follows the early days of the puerperium or the cessation of nursing.

The control group of 128 mothers, 25 per cent, were given the camphor medication and supportive treatment outlined in the third paragraph. In previous experience, we had found this method to be satisfactory in all respects except for its failure to control the discomfort experienced by these mothers during the hospital stay. This major drawback was shown in the high percentage—57—of women who complained rather bitterly of the pain associated with engorgement of the breasts during the "drying-up" phase, which often lasted throughout the time the patient was hospitalized after delivery. Its major advantage lies in the permanence with which breast difficulties were alleviated and with the minimal number of women, approximately 18 per cent, who experienced such symptoms after leaving the hospital.

Among the 48 per cent, 238 women, in whom lactation was suppressed with the use of ethinyl estradiol, there was no drug sensitivity or unpleasant side effect. Its greatest success was with the control of pain and engorgement of the breasts during the hospital period, when only 34 per cent had painful discomfort and only 26 per cent showed breast engorgement. Since so many of our mothers fail to nurse their offspring (even after exhaustive exhortation by us), this one feature of ethinyl estradiol affords such women the most comfortable puerperal convalescence possible. However, upon release from the hospital, this same group showed the highest percentage of continued difficulty at home, with 60 per cent showing formation of milk

with free leakage, 46 per cent having breast engorgement and 43 per cent complaining of pain in the breasts. Additional therapy was required in the form of breast binding and restriction of the fluid intake for almost one-half of these 238 women. The return to the camphor regimen was required for pain in 34 per cent of the number, camphor being used after discharge from the hospital because of the previously mentioned difficulties in the supply of ethinyl estradiol. The increased postpartum and withdrawal bleeding experienced with the use of stilbestrol did not occur with ethinyl estradiol. There was no evidence of a heavier bloody lochia during the time of administration in the hospital (the major objection to stilbestrol) nor was the occurrence of withdrawal bleeding of significant frequency judging from information acquired by routine questioning during postpartum visits.

SUMMARY AND CONCLUSIONS

In this series of 501 consecutive private cases at the Newark Beth Israel Hospital, lactation was inhibited or controlled by the use of ethinyl estradiol more successfully than by any other means previously employed. During the hospital stay of the puerperal women, pain and engorgement in the breasts were most effectively relieved by this medication, whereas a camphor regimen with other supportive therapy was highly ineffectual during the same period. There was no increase in the amount of blood in the lochia while under this estrogen medication and the number of instances of recognizable withdrawal bleeding was so small as to be negligible.

The high percentage of non-nursing mothers, who experienced difficulties with their breasts after omission of ethinyl estradiol on the sixth to the ninth postpartum day, could be reduced to a minimum if this medication were available to them after leaving the hospital. When it was not available, the regimen of camphor, saline purges, breast binding and limitation of fluids appeared to be more successful in this respect only.

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. W. H. Stoner, Medical Research Division, Schering Corporation, for his active interest and also, to the Schering Corporation for the ethinyl estradiol (Estinyl) supplied in this study.

ADDENDUM

Since completion of this paper, ethinyl estradiol in a dosage of 0.15 mg. daily has been used with equal success and will be the subject of a future report.

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COMPARATIVE EFFECT OF SYNTHETIC ESTROGENIC SUBSTANCES ON THE POSTPARTUM BREAST

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A NUMBER of synthetic estrogenic substances have been shown to prevent engorgement in the human breast (1, 2, 3). Apparently the clinical result is produced indirectly by an inhibitory effect on the pituitary gland (4).

With the increasing trend to bottle-feed rather than breast-feed babies, it is important that the hormonal agents used to inhibit mammary engorgement be properly evaluated with regard to their physiologic effect. The purpose of this communication is to compare the clinical effect of the recently available estrogen, dienestrol,[1] with that of diethylstilbestrol and alpha-estradiol on the postpartum breast of non-nursing mothers.

MATERIAL AND PROCEDURE

Three hundred and seventy-four mothers who did not elect to nurse their babies, or whose babies died, or in whom maternal disease precluded nursing, comprise the patients studied. Two hundred and thirty-one were included in previous reports (5, 6). Approximately 60 per cent of the 93 controls, and those given diethylstilbestrol (95 women) and alpha-estradiol (61 patients) and 30 per cent of those given dienestrol (125 women) were primigravidas. The age range was 14 to 48 years, with the average nearly 20 years.

When administered, treatment was begun one-half to seventy-five hours postpartum for the entire group, and within twenty-four hours for all but 60 women.

Diethylstilbestrol was usually given orally once daily as enteric coated tablets in amounts of 5 to 10 milligrams per day for one to seven days. The dose of alpha-estradiol ranged from 0.5 to 2.5 milligrams and was administered orally in propylene glycol at fairly regular intervals during the twenty-four hours for four days. The amount of dienestrol given orally ranged from 0.5 milligram daily to 0.6 milligram three times a day for three to nine days. All patients who took dienestrol were instructed to report by telephone if mastalgia appeared after their discharge from the hospital. Medication was given by one of four physicians and objective results on the breast checked by one of the two present writers.

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[1] The dienestrol was supplied through the courtesy of Ortho Products Inc., Raritan, N. J.

Results were described as good, fair, or failure. A good result indicated there was no pain; fair, discomfort persisted twelve hours or less; and failure meant there was no apparent diminution in breast engorgement and mastalgia at the usual time lactation begins, three to five days postpartum.

RESULTS

It was found that diethylstilbestrol given in total doses of 40 milligrams over a four to five day period usually prevented breast engorgement and mastalgia. A comparable number of units of alpha-estradiol gave few good results whereas dienestrol in amounts of 1.0 milligram daily for five days, produced effects almost as good as with the use of diethylstilbestrol (Table 1). On the other hand, in contrast to diethylstilbestrol, engorgement did not appear after discontinuing dienestrol. Medication administered more than once a day, or in greater initial doses did not improve the results ap-

Table 1. Results in the Prevention of Breast Engorgement and Mastalgia

Effect	Method of treatment			
	Diethyl-stilbestrol	Alpha-Estradiol	Dienestrol	Control
Good	60	23	62	4
Fair	24	24	49	1
Failure	11	14	14	88
Per cent failure	11.6	22.9	11.2	94.6

preciably with either diethylstilbestrol or dienestrol, but did with alpha-estradiol. The three drugs did not prevent lactation. There was usually, however, a delay or a decrease or both in the amount of milk flow, but the impression was gained that this was largely due to removal of the stimulus of sucking. Generally, the outcome was more favorable if medication was started within twenty-four hours after delivery. There was neither toxic effect nor any increase in lochia rubra from administration of any of the drugs in the doses used. There was no appreciable difference in results with regard to parity, race or age.

COMMENT

It is worthwhile to point out that breast engorgement and lactation are apparently independent of one another. Engorgement is caused by lymphatic and vascular stasis, not by distention of the ducts with milk (7). Meites and Turner (4) have rightly criticized the clinical work done to determine the effect of various hormones on the postpartum breast. Much of it has been uncontrolled. It is not fully recognized by some clinicians that to maintain lactation the neurogenic reflex initiated by sucking is at least

as important, if not more so, than the hormonal action. Ordinarily the duration of engorgement that accompanies the onset of lactation averages 24 to 36 hours. On the other hand, if breast nursing is to be discontinued, but the breast is still emptied at irregular intervals, the period of engorgement is likely to be prolonged. Supposedly sucking acts as a powerful stimulus to release the lactogenic hormone from the pituitary (4, 7). Therefore best results are obtained, when lactation is undesired, by eliminating mechanical massage and the emptying of the breast.

In our experience it was apparent that the use of synthetic estrogenic substances given shortly postpartum and continued for four to five days did diminish or prevent breast engorgement in a majority of non-nursing mothers. The effects produced by small doses of dienestrol compared favorably with those of the more extensively used diethylstilbestrol and were superior to those of alpha-estradiol. Moreover, the effect was more permanent. This latter finding marked an advantage over diethylstilbestrol, which sometimes merely postponed engorgement (5, 7, 8).

SUMMARY

A comparative controlled study was made using 374 non-nursing mothers to determine the clinical effects of dienestrol, diethylstilbestrol and alpha-estradiol on breast engorgement postpartum. It was found that dienestrol, in the dose employed, was practically as effective as diethylstilbestrol in preventing breast engorgement postpartum. Alpha-estradiol was comparatively ineffective. Dienestrol had the advantage that breast engorgement seldom recurred after it was discontinued, whereas recurrence was frequent after administration of diethylstilbestrol.

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LETTERS TO THE EDITOR

TO THE EDITOR:

EFFECT OF ALPHA TOCOPHEROL IN DIABETES MELLITUS

FOR the last two years the author has been one of a group (1), including Dr. Floyd Skelton, treating various types of cardiovascular disease with large doses (200 to 400 mg. daily) of alpha tocopherol (Vitamin E). It was noted that patients who also suffered from diabetes mellitus would sometimes become weak and experience mild insulin reactions after a week or two on this regime. The dose of insulin required became somewhat lower, and then seemed to be maintained for many months at this new level. This observation has been substantiated by several of my colleagues, notably Dr. W. E. Shute and Dr. George Dowd, and made the basis of our cautious management of diabetic cardiac patients receiving large doses of alpha tocopherol (2).

Several of my patients however, after six months to a year of such therapy, were able to discontinue the use of insulin altogether (3).

One patient, a nine-year-old male, had been getting progressively larger doses of insulin for three years. It required a total of 60 units per day to control the diabetes. During the administration of 270 mg. of alpha tocopherol he was able to reduce the insulin to 5 units per day and was free from glycosuria in two and one-half weeks. His diet was unaltered throughout.

The mechanism of this effect is not obvious. Clinically one might infer that there were two distinct phases:

a) An immediate "reinforcing" effect upon the insulin, possibly related to liver metabolism.

b) A delayed effect, occurring slowly over a period of months, in which the blood supply to the islet tissue of the pancreas is greatly improved.

There may also be an effect on glycogen storage in the liver and muscles, since juvenile patients as well as those with arteriosclerosis appear to respond well. Our experience with arteriosclerotic peripheral vascular disease (4) would lend some support to the first of these conceptions.

Only recently the author became aware of the work of Butturini (5) in Italy. He has been investigating the effect of alpha tocopherol on hyperglycemia since 1943, and is able to discontinue insulin in the treatment of mild diabetes if alpha tocopherol is administered in doses of 50 to 60 mg. per day, by intramuscular injection. In our series all alpha tocopherol was

administered by mouth in much higher doses, and in general, the cases seem to be more severe than those of Butturini.

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TO THE EDITOR:

THE INTRAORAL ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE TABLETS IN THE TREATMENT OF ADDISON'S DISEASE

THE intraoral administration of desoxycorticosterone acetate (DCA) has been the method of choice in the treatment of Addison's disease in the medical clinic of the University of California Hospital since 1940 (1). Until recently the preparation used was DCA dissolved in a mixture of 80 per cent propylene glycol and 20 per cent absolute alcohol; it was given by drops under the tongue. This sublingual method proved highly effective, but meticulous care had to be taken in the handling and administration of the solution of DCA. If the solution was cooled to a low temperature, for instance if the patient kept his supply of hormone in the refrigerator, the DCA tended to crystallize; or if the propylene glycol-alcohol mixture was exposed to the air, being highly hygroscopic, it absorbed sufficient water to lead to precipitation of the hormone. It is well known that the undissolved DCA is not readily absorbed through the mucous membrane of the mouth. If the sublingual dose exceeded 0.1 cc. (4 drops) of solution there was a tendency to swallow some of it. DCA has very little effect when ingested (2).

The disadvantages of using propylene glycol-alcohol as a solvent for DCA have been overcome by employing as a solvent a polyethylene glycol wax of high molecular weight, which is solid at body temperature. The DCA was dissolved in the melted wax; the material was then cooled and made up into tablets containing 2.0 mg. of hormone. The wax is virtually tasteless and there is no apparent toxicity in the amounts used (3). When placed inside the cheek the tablets slowly disappear in the course of an hour.

Since 1946 the patients with Addison's disease who have been under observation in the medical clinic, 14 in all, have been treated with the intraoral tablets of DCA. The criteria for judging the maintenance dose of the hormone were the patient's sense of well being and his capacity to carry on his usual occupation. A summary of the treatment of these patients is given in Table 1. The average daily dose of DCA was 4.5 mg. None of these patients received supplementary salt.

TABLE 1

Patient	Age	Sex	Duration of disease. Years	Previous treatment DCA solution, sublingual		Present treatment DCA tablet, intraoral	
				Mg./day	Years	Mg./day	Months
F.T.L.	59	M	1	0	0	2	12
H.H.	53	F	4	5	2	4	24
H.A.H.	31	F	5½	4	3	4	12
F.F.	55	M	4	4	2⅓	4	14
A.C.P.	54	M	3	3	1	6	6
D.M.W.	73	M	8	6	7	6	12
I.O.P.	38	M	7	4	5	4	14
F.D.	45	F	5	4	2	4–6	14
R.W.M.	47	M	5	5–6	3	6	16
H.C.L.	47	F	4	3–5	½	6	15
M.F.McN.	41	F	2½	0	0	4	11
S.T.B.	18	M	1	0	0	4	9
B.C.R.	55	F	7	4	4	4	12
H.L.	39	M	12	5	7	4	12

It has been the experience in this clinic that the maintenance dose of DCA when using the propylene glycol-alcohol solution sublingually, approaches the dose required when the DCA is given intramuscularly, the ratio of the doses by the two methods being somewhat less than 2 to 1 (1). The intraoral tablet appears to be equally as effective as the sublingual solution. A more complete report of the data is in preparation.

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The Association Postgraduate Course In Endocrinology

THE Postgraduate Committee of THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, under authority of its Council, announces a course of lectures and demonstrations in CLINICAL ENDOCRINOLOGY to be held in OKLAHOMA CITY at the SKIRVIN HOTEL, FEBRUARY 21 to 26, inclusive, 1949.

The faculty will consist of the most prominent investigators and clinical endocrinologists in the various branches of the medical sciences in the United States and Canada.

It is the intent of the Committee that this course be a practical one of interest and value to both the GENERAL PRACTITIONER AND THE SPECIALIST.

A fee of $100 will be charged for the entire course and the attendance will be limited to 100. Registration will be in the order of checks received. Should there be an insufficient number of applicants to warrant the course, the registration fee will be immediately refunded in full.

Please make your application on your letterhead and forward, together with your check payable to THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, to DR. HENRY H. TURNER, CHAIRMAN OF THE POSTGRADUATE COMMITTEE, 1200 NORTH WALKER STREET, OKLAHOMA CITY 3, OKLAHOMA.

Due to other meetings being held in Oklahoma City at the time of this assembly, satisfactory hotel accommodations will be difficult to procure on short notice; therefore, it is suggested that all applicants MAKE THEIR RESERVATIONS EARLY.

SOME OF THE BETTER DOWNTOWN HOTELS IN OKLAHOMA CITY ARE: Biltmore, Black, Huckins, Skirvin, Skirvin Tower, Wells-Roberts.

The 1949 Meeting of the Association for the Study of Internal Secretions

The 31st Annual Meeting of the Association for the Study of Internal Secretions will be held at Haddon Hall, Atlantic City, New Jersey, June 3 and 4, 1949.

Inasmuch as the American Medical Association will be meeting in Atlantic City the following week, it is extremely important that hotel reservations be made at once directly with the hotel.

Further details concerning the meeting will be published at a later date.

The Awards of the Association for 1949

Nominations for Awards

Three Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each Award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1949.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori and in 1948 to Dr. Fuller Albright. No award was made in 1943. No age or special limitation is stipulated by the donor of the Award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or preclinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li and in 1948 to Dr. Carl G. Heller. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947 and in 1948 it was given to Dr. Ernest M. Brown,

Jr. This Fellowship is designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. The Fellowship may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend for the Fellowship will vary in accordance with the qualifications of the appointee, but will not exceed $2500.00. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals, submit a program of proposed study, indicate one or more institutions where the proposed program shall be carried out and submit statements of approval from the investigators with whom he proposes to conduct his research.

Award of the American Goiter Association

THE VAN METER PRIZE

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Madison, Wisconsin, May 26, 27 and 28, 1949, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy should be sent to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than March 15, 1949. The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association. This will not prevent its further publication, however, in any journal selected by the author.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: ROY HERTZ. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS

PITUITARY

GRANT, F. C.: Surgical experience with tumors of the pituitary gland, *J.A.M.A.* **136:** 668 (March 6) 1948.

Of the brain tumors verified on the neurosurgical service of the University and Graduate hospitals of the University of Pennsylvania, 10 per cent were tumors of the pituitary gland. A useful analysis of the results of surgical and/or x-ray treatment of 101 cases of pituitary tumor is given. In three of four cases of diabetes insipidus relief was obtained by operation. In no case of craniopharyngioma was there improvement of symptoms related to the endocrine glands. X-ray was ineffective and operation, undertaken only because of serious loss of vision, was fatal in about 30 per cent of cases. There were 71 cases of adenoma. Ten of these were eosinophilic in type. By combined x-ray and surgical treatment, progression of symptoms (of acromegaly) was usually halted. In only three cases of adenoma were endocrine functions which had been lost (menstruation, potency) restored. Most of the fatalities in all types were in the first few postoperative days and resulted from acute or chronic panhypopituitarism ("acute glandular failure"). Death occurred either immediately or after a few days of coma, usually with hyperthermia. There were no fatal results of operation in cases of eosinophilic adenoma.—*A.P.E.*

THYROID

MUSSEY, R. D.; HAINES, S. F., and WARD, E.: Hyperthyroidism and pregnancy, *Am. J. Obst. & Gynec.* **55:** 609–619, 1948.

The authors treated hyperthyroidism during 30 pregnancies in 29 women. In those with exophthalmic goiter, 3 received iodine alone; 16 iodine and thyroidectomy during pregnancy; 1, iodine, thiouracil and thyroidectomy during pregnancy; and 1 had a spontaneous abortion before treatment. Iodine and thyroidectomy during pregnancy were used in 8 patients who had adenomatous goiter, and 1 aborted spontaneously before treatment. The outcome of pregnancy is known in 20 instances: 16 full term deliveries, 2 spontaneous abortions before any treatment, 1 premature birth with neonatal death, and 1 spontaneous abortion 8 days after thyroidectomy. The authors are of the opinion that the standard treatment of hyperthyroidism by iodine and thyroidectomy can be carried out safely in the great majority of cases of hyperthyroidism complicating pregnancy.—*C.D.D.*

PARATHYROIDS

STEPHENSON, H. U., JR., and MCNAMARA, W. L.: The parathyroid: a study based, in part, on sixty post-mortem examinations with presenta-

tion of a case of hyperfunctioning adenoma, *Am. J. M. Sc.* **215:** 381, 1948.

The authors present a review of the historical, embryological, anatomical, histological, pathological, and clinical aspects of the parathyroid glands and their disorders largely from a survey of the literature. In addition, the histological features were amplified by post-mortem examinations of sixty patients. Illustrations are given of sections a "degenerated parathyroid," and an irradiated parathyroid gland. A case history hyperparathyroidism with minimal bone disease and with extensive renal disease and phosphate retention associated with a parathyroid adenoma and including necropsy findings is reported.—*E.C.R., Jr.*

ADRENALS

BURRAGE, W. C., and HALSTED, J. A.: Adrenal medullary tumor (pheochromocytoma); case report with successful operation, *Ann. Int. Med.* **28:** 838–849, 1948.

Fifty-one cases of pheochromocytoma have been previously reported in the literature. The authors report the fifty-second. Three were malignant and there were 11 postoperative deaths. The authors confirm the value of the response to histamine phosphate as a diagnostic procedure. One-half milligram of histamine phosphate was injected subcutaneously and within ten minutes the blood pressure rose from normal to systolic 260 and diastolic 160, with a pulse rate of 140 beats per minute. The authors advise caution in the use of this drug in patients suspected of having a pheochromocytoma.—*C.D.D.*

HOYNE, A. L., and BROWN, R. H.: 727 Meningococcic cases: an analysis, *Ann. Int. Med.* **28:** 248–259, 1948.

Among 727 meningococcic patients, ranging in age from 7 weeks to 71 years, the authors report 108 deaths, or a fatality rate of 14.8 per cent. Sixty-seven were moribund on admission, and among these, 20 gave clinical and 11 pathologic evidence of the Waterhouse-Friderichsen syndrome. The authors were impressed by the number of times the clinical picture strongly resembled the Waterhouse-Friderichsen syndrome, and autopsy disclosed no gross or microscopic pathologic changes in the adrenals. They suggest this may explain some of the reported recoveries in which the Waterhouse-Friderichsen syndrome was diagnosed.—*C.D.D.*

PERERA, G. A.: Effect of continued desoxycorticosterone administration in hypertensive subjects, *Proc. Soc. Exper. Biol. & Med.* **68:** 48–50 (May) 1948.

Two men and three women with uncomplicated hypertensive vascular disease were observed. All subjects were maintained on a constant dietary, fluid and sodium chloride intake. Four received DCA subcutaneously at the rate of 10 mg. daily for 30 days and a fifth patient received 20 mg. daily for 50 days. The daily injection of DCA produced a transitory rise in "resting" blood pressure in all instances and a sustained increase during the period of drug administration in three of the five subjects. There was a progressive drop in serum potassium concentration, an increase in carbon dioxide content and a fall in chloride concentration. Salt and water retention was observed only during the first

7 to 10 days of treatment, with reversal to control levels thereafter. The author reported that the pressor action of DCA does not appear to be due to a direct humoral mechanism dependent on its concentration in the circulation.—*F.N.A.*

GONADS

BLOOM, O. H.: Mixed synthetic estrogens—their use in the menopause, *Am. J. Obst. & Gynec.* **53**: 263–265 (Feb.) 1947.

The author reports on the use of mixed synthetic estrogens in a group of 105 climacteric patients. The present method of therapy consists of weekly injections of 15 milligrams of dimethoxystilbestrol in combination with 1.0 milligram of diethylstilbestrol in oil, for 3 weeks. The author believes this combination more effective than larger single doses of either drug. This phenomenon is explained on the basis of synergistic action between the two preparations.—*C.D.D.*

FINKLER, R. S., and BECKER, S.: A preliminary evaluation of dienestrol in the menopause, *Am. J. Obst. & Gynec.* **53**: 513–519 (March) 1947.

Dienestrol, which differs chemically only slightly from hexestrol and stilbestrol, was evaluated clinically in 70 climacteric patients. Their ages ranged from 32 to 65 years and averaged 48.5 years. The dosage varied from 0.2 to 1.5 milligrams. The patients all reported quick and full relief, a sense of well-being, allayed apprehension and renewed energy.

The untoward effects were as follows: slight nausea during therapy, 3 patients; symptoms of pelvic congestion when therapy was continued over long periods of time, 5 patients; withdrawal bleeding, 2 patients.

Vaginal smears were done in all patients before and after therapy. In general, the vaginal response paralleled the clinical response but it is interesting to note that 15 of these patients had nonestrous or low estrous smears after therapy.—*C.D.D.*

FREMONT-SMITH, M., and MEIGS, J. V.: Menstrual dysfunction due to emotional factors, *Am. J. Obst. & Gynec.* **55**: 1037–1043, 1948.

The authors report the sudden cessation of uterine bleeding of five months' duration in a 26-year-old single girl following a 3-hour discussion period during which her guilt and anxiety were partially relieved. Various gonadotropin fractions, and progesterone, had previously been ineffective. Several endometrial biopsies were taken and two of these were secretory in type. The patient has since continued to bleed cyclically and normally for nine years. The authors make a plea for study at the emotional level before destructive surgery is undertaken in young women with prolonged uterine bleeding.—*C.D.D.*

RANDALL, L. M.: The treatment of amenorrhea in young women, *Am. J. Obst. & Gynec.* **53**: 453–458 (March) 1947.

Eighty-seven patients, ranging from 19 to 25 years of age, who had amenorrhea for a year or longer, were treated by a combination of methods. Those with anorexia nervosa were treated with a gradually increasing caloric intake until 3,400 to 3,600 calories per day were taken. Those with atrophic endometrium or considerable reduction in uterine size were given oral estrogens in cyclic dosage. Thyroid extract was used to raise the

basal metabolic rate to normal. Low dosage roentgen-ray irradiation to the pituitary body and/or the ovaries was used in selected patients. Gonadotropic therapy was employed in only 3 patients.

The results of various combinations of the above therapies were as follows: in 17 patients whose amenorrhea was due to failure ovarian function, 10 had return of menses; in 36 with amenorrhea associated with pituitary failure, 26 responded to treatment; in 15 who had anorexia nervosa, uterine bleeding was initiated in 8; and in 19 with primary amenorrhea, 3 patients, whose ages were 19, 19 and 21 respectively, began to have menses after treatment.

The follow-up period ranged from 1 to 6 years, with an average of 2 years and 3 months. However, no statements are made as to how regular the menstrual cycles were in these patients or how long the cycles remained after discontinuation of therapy.—*C.D.D.*

STROMME, W. B.: True hermaphroditism, *Am. J. Obst. & Gynec.* **55:** 1060–1064, 1948.

The author reports the thirty-ninth instance of true hermaphroditism. A large penile clitoris, measuring 5 centimeters in length was present. No corpus cavernosum urethra was found, and the external urethral meatus was at the base of the penile clitoris. The external genitalia were otherwise female in appearance. The vagina was $6\frac{1}{2}$ centimeters in length and there was a small cervix. No testicular tissue was palpable. At laparotomy, an infantile uterus was seen and a biopsy specimen was taken from each of 3 areas which were considered gonadal in nature. Microscopic study revealed both ovarian and testicular tissue to be present. At the patient's request and as a result of psychiatric consultation, a second laparotomy was performed and all ovarian tissue was removed. The patient, who had been brought up as a female, made a very satisfactory readjustment to the chosen male status. The patient has since married.—*C.D.D.*

WOLFE, S. A., and NEIGERS, I.: The effect of equine gonadotropin (gonadogen) on the human ovary, *Am. J. Obst. & Gynec.* **55:** 979–991, 1948.

Twenty women, varying in age from 25 to 49 years, were given equine gonadotropin intramuscularly, usually 60 units, over a variable period of time prior to laparotomy for fibromyomata. The drug was administered in the first half of the menstrual cycle in 5 patients, in mid-cycle in 4, and in latter part of the cycle in 12 patients. Microscopic study of the ovarian tissue removed revealed the following changes which the authors considered were attributable to the equine gonadotropin: 1) In the current follicle, the granulosa cells were enlarged and clear, simulating the lutein type of cell. 2) Hypertrophy and hyperplasia of the theca interna layers was the most marked effect. 3) Vascular engorgement was prominent and accounts for the hypertrophy of the granulosa and theca interna cells. No evidence of inauguration of follicle maturation or rupture was produced by equine gonadotropin.—*C.D.D.*

ZELLE, K.: Arrhenoblastoma of the ovary, *Am. J. Obst. & Gynec.* **55:** 869–874, 1948.

The author reports an arrhenoblastoma of the ovary in a 23-year-old patient. She had had a child two years previously. Normal menstrual cycles returned following delivery, but gradually her bleeding became more and more frequent, finally progressing to continuous spotting. However, for one year prior to surgery she had been amenor-

rheic. The usual picture of virilism was present. The ovarian tumor removed weighed 14 pounds and had cystic and solid areas. A small amount of ovarian stroma was found along the periphery. This tissue contained corpora albicantia, but no primordial follicles. The tumor showed a wide range of morphologic structures, but 2 types of cells predominated. These were spindle shaped cells with scant cytoplasm and oval vesicular nuclei, which in places were arranged as rete-like structures; and medium sized polygonal, oval or round cells, with a coarse granular nuclei and a moderate amount of neutrophilic cytoplasm. Mitotic figures were rare. Evidences of degeneration were common. The multiplicity of tissue elements suggest the possibility of a teratomatous origin. Periods returned 4 months after operation, and in 8 months most of the hirsutism had disappeared.—*C.D.D.*

PANCREAS

FRANKS, M.; BERNS, R. F.; KAPLAN, N. O., and MYERS, G. B.: Metabolic studies in diabetic acidosis. II. The effect of the administration of sodium phosphate, *Arch. Int. Med.* **81**: 42–55, 1948.

The authors present phosphorus, glucose, water and chloride balance studies in 10 patients with severe diabetic acidosis. Five patients received 1,319 milligrams of phosphorus within 24 hours after the first administration of insulin. Another 5 received 2,638 milligrams of phosphorus. The first group retained 95 per cent and the second 85 per cent of the phosphorus. Despite this, plasma inorganic phosphorus levels fell to the subnormal range in most of the patients. The results are compared with a control group who received no sodium phosphate. The authors believed that sodium phosphate administration is accompanied by (a) tendency toward improved utilization of carbohydrate, (b) a rise in plasma chloride and in carbon dioxide combining power, (c) an apparent retention of fluid in the vascular system, (d) a rapid clearing of the mental state, and (e) a statistically significant decrease in fatality rate. The authors believe that their studies show that the therapeutic regimen in diabetic coma should include the parenteral administration of sodium phosphate four to eight hours after the first dose of insulin.—*C.D.D.*

GENERAL

ARAGON, GLORIA T.: An evaluation of plasma pitocinase determination in the toxemia of pregnancy, *Am. J. Obst. & Gynec.* **55**: 961–966, 1948.

Pitocinase determinations, using the method of Page, were done 83 times on 50 pregnant patients, 33 of whom were toxemic. The enzymatic nature of the pitocin inactivation by pregnancy serum was confirmed. The author found no significant difference in pitocinase values in hypertensive and pre-eclamptic patients. No correlation was found between the pitocinase levels and the clinical course of the toxemia and the hypersensitivity of the patient to pituitrin, as determined by the pituitrin test. It is concluded that plasma pitocinase levels in the toxemia of pregnancy are of no prognostic or diagnostic value.—*C.D.D.*